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Original Communications

NUTRITION STUDY IN PREGNANCY*

DIETARY ANALYSES OF SEVEN-DAY FOOD INTAKE RECORDS OF 514 PREGNANT WOMEN, COMPARISON OF ACTUAL FOOD INTAKES WITH VARIOUSLY STATED REQUIREMENTS, AND RELATIONSHIP OF FOOD INTAKE TO VARIOUS OBSTETRIC FACTORS

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(From the Prenatal Clinics of the Presbyterian, Jewish and Philadelphia General Hospitals)

THE dietary inadequacies discovered among the pregnant women in a group of patients followed at the Dental School of the University of Pennsylvania served as a stimulus to study the actual food intake of a large number of pregnant women in Philadelphia. We thought it well to compare the food intake of these women with the variously stated allowances for pregnancy. We wished also to determine any possible relationships between dietary adequacy and various obstetric factors, and complications of pregnancy.

Our interest was further encouraged by the admission of a ward patient with marked clinical pellagra, beriberi, and scurvy at the sixth month of her first pregnancy. These conditions had developed during a period of two months of abstinence from all protein food and vegetables, unfortunately following medical advice. On appropriate vitamin ther-

*This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.

Read, by invitation, at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 3, 1941.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

apy the patient made a quick recovery, was observed in the clinic, and delivered at term a living child, whose weight was slightly over five pounds.

CASE MATERIAL

The study included 514 women. They were selected in a general manner to represent several population, economic, racial, and nationality groups. White women were chosen from the prenatal clinics of the Jewish Hospital, Presbyterian Hospital and the Philadelphia General Hospital. White women from the private practices of three Philadelphia obstetricians, and Italian women from the Starr Centre Prenatal Clinic were also included.

This group represented many sections of the City of Philadelphia and was regarded as appropriate to the problems encountered at the three hospitals. Statistically, however, the sampling was not accurate for the city as a whole. There was too large a percentage of negroes,

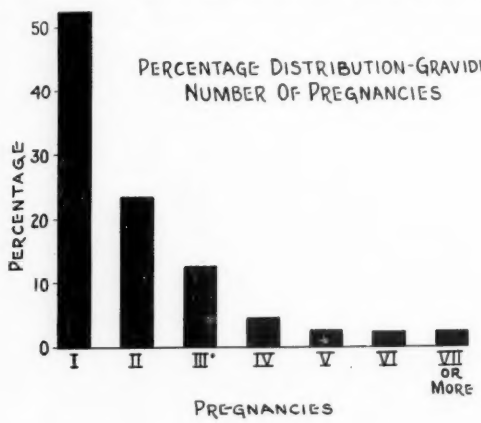


Fig. 1.

too large a proportion of women in the lower age groups, too great a percentage of primigravidas, and, finally, a disproportion between negroes and foreign-born. Probably too many were in the relief class, but at the time this study was begun the proportion, particularly among the negroes, was not as far wrong as it would be today.

ANALYSIS OF THE CASE MATERIAL

There were 382 (74.3 per cent) white women and 132 (25.7) negro women; 436 (84.9 per cent) ward and 78 (15.1 per cent) private patients. By order of pregnancy 271 (52.7 per cent) were primigravidas, 121 (23.5 per cent) secundigravidas, 65 (12.6 per cent) tertigravidas, and 57 (11.2 per cent) other multigravidas, including five who had been pregnant ten or more times (Fig. 1). By stage of gestation, 42 (8.1 per cent) women were in the first trimester; 243 (47.2 per cent) women were in the mid-trimester; 96 (18.7 per cent) women were in the seventh month; 81 (15.9 per cent) women were in the eighth month, and

52 (10.1 per cent) women were in the ninth (Fig. 2). Four hundred and twenty-six (83 per cent) women were American born; 88 (17 per cent) were foreign born; of the latter group 62 (12 per cent of the total) were Italian.

Age groups showed the following divisions: 20 years and under; 138 (26.8 per cent); 21 to 25 years, 152 women (29.6 per cent); 26 to 30 years, 112 women (21.8 per cent); 31 to 35 years; 72 women (14.0 per cent); 36 years and over, 40 women (7.8 per cent) (Fig. 3).

In the 243 parous women, 71 (29 per cent) had had complications in previous pregnancies, while 48 women (19.8 per cent) had had abnormal labors.

The economic status of these women was classified by the income per capita per week, obtained by dividing the total weekly income by the number of persons in the family. Stiebeling and Phipard[1] investigated

Fig. 2.

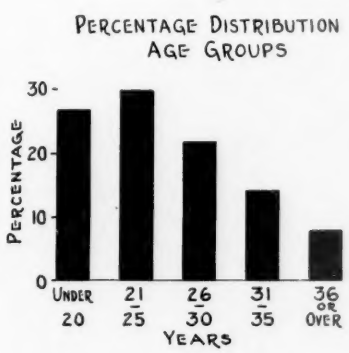


Fig. 3.

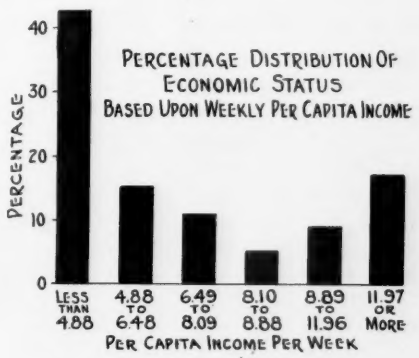


Fig. 4.

the relationships between food expenditures and income for families in various areas, basing income groups on specified sums spent for food. We applied their findings for the North Atlantic area; the groups from lowest to highest, by per capita income per week for white and negro women are shown in Fig. 4. A large proportion of the negro women (82 per cent) were in the lowest income bracket. The economic status of the white patients has been classified in Table I.

Fifty-five women (10.9 per cent), not including those with more than one complication, had toxemias of late pregnancy, characterized by albuminuria, edema, severe headaches, or hypertension. Six (1.2 per cent) women had thyrotoxicosis, mostly of mild degree. Ten (2 per cent) women had ante-partum hemorrhage, placenta previa, or premature separation of the placenta. Pyelocystitis was an ante-partum

TABLE I. ECONOMIC STATUS (WHITE WOMEN)

WEEKLY PER CAPITA INCOME	NUMBER OF CASES	PER CENT OF WHITE WOMEN
Less than $4.88	111	29.1
$ 4.89 to $ 6.48	64	16.8
$ 6.49 to $ 8.09	49	12.8
$ 8.10 to $ 8.88	25	6.5
$ 8.89 to $11.96	44	11.5
$11.97 and over	89	23.3
	382	100.0

complication in 5 patients (1 per cent), and an equal number had pelvic infections, i.e., reactivation of old salpingitis. Twenty-five other women (5 per cent) had medical complications of various types. Where multiple complications were present, toxemia was always a factor. The histories of the present pregnancies showed that at least 20 per cent of the patients had suffered moderate to marked nausea and vomiting. A similar distribution of other minor symptoms of early toxemia, such as paresthesias and muscle cramps, was recorded.

The present pregnancy, 502 deliveries reported, ended in spontaneous delivery in 366 (72.9 per cent) women. Forceps deliveries, mostly prophylactic low or perineal forceps, terminated 100 (19.9 per cent) of the cases. There were 14 (2.8 per cent) breech deliveries, while cesarean section was resorted to in 19 women (3.8 per cent). Three other operative deliveries were recorded: internal podalic version, supravaginal hysterectomy, and cesarean section, on account of leiomyomas and an operative dilatation of the cervical canal.

Of the 502 deliveries reported, 476 infants (95 per cent), were normal at birth. There were 4 stillbirths. Fourteen babies died during the mother's stay in the hospital. There were 5 pairs of twins, and 2 monsters. One stillbirth was premature and 10 neonatal deaths occurred in premature infants.

The child's weight was not recorded in 20 cases. Twenty-nine (5.8 per cent) of the babies weighed less than 2,500 Gm. Two hundred and seventy-eight (56.3 per cent) showed between 2,500 and 3,499 Gm.; 144 (29.2 per cent), 3,500 to 3,999 Gm.; and 43 (8.3 per cent), 4,000 to 5,400 Gm.

Forty-seven of the women (9.4 per cent) presented sufficient febrile reaction of pelvic origin in the puerperium to be regarded as morbid, according to the standard proposed by the American Committee on Maternal Welfare.[2] Extragenital infections accounted for puerperal morbidity in an additional 24 (4.8 per cent) women.

In a total of 483 cases in which information was obtainable regarding lactation, 339 mothers (70.2 per cent) breast fed their offspring. Eighty-five (17.6 per cent) of the babies were formula fed during their stay in the hospitals, while 59 (12.2 per cent) were on breast feeding with supplemental formula.

METHODS OF COLLECTING DATA

Methods of collecting dietary information fall into two major categories: (1) Those methods which make use of weighed diets and (2) those which depend upon the estimation of foods actually eaten.

There are, of course, variations in each classification. Weighed diets have many advantages. They are accurate, and they minimize human errors, especially, those due to lack of intelligence in the subjects studied. Measured diets are economical and practical. Many patients do not use scales accurately without supervision, and many are too poor to own or buy them. There are various forms of measured diets. They extend from the very general method of checking food by articles rather than by servings, to the more precise method of measuring foods with ordinary household equipment.

There are several types of food records which employ the measured diet method and which rely upon the memory and integrity of the patient for information. Some are questionnaires, filled out by the worker as she questions the informant regarding her food intake for one or two days. Others are more general and require the patient only to list the number of servings, daily or weekly, of various classes of food. Still others cover a longer period of time and seek meal-to-meal information. These emphasize food actually eaten, rather than food purchased, and give a better picture of the individual's food habits. If the patient records the meal immediately after she has eaten it, the possibilities of omission are lessened. Again, those food records which cover a longer time naturally give more information about food habits.

The food record form which we used was designed to include space for all food eaten during seven days. A nutritionist explained to each woman how to fill in the record properly. She was instructed to write down in detail all foods eaten each day, including regular meals and all food taken between meals. The kinds of each food were to be specified, as well as the amounts in household measures. Milk and other liquids of food value were measured in an eight-ounce measuring cup and recorded in ounces. To illustrate the method, all foods eaten during that day up to the time of the interview were recorded for the patient. Her weight and height, without shoes, were recorded at the first visit. When she returned the food record after seven days, all items were checked carefully with her and necessary corrections or additions were made. The record was then analyzed and the food values were obtained chiefly from "Food Values of Portions Commonly Served."[3] By dividing the total value of the food record by seven, we were able to obtain the average daily food intake of each patient.

At the outset of the study in 1939, the vitamin A and the vitamin C values expressed in international units were not available for a great many foods, and those figures which were available presented wide ranges of variation. It was then decided to use the values expressed in Sherman units for vitamins A and C without attempting to convert them into international units. Later, however, when the analyses had been complete, we applied the conversion factors employed by Stiebeling and Phipard in order to make the study more comparable with the

findings of other surveys. Vitamin A values were divided by 2 to obtain international units, and vitamin C values were multiplied by 10. Twenty Sherman units per milligram were allowed when converting these figures to ascorbic acid. The values for vitamin B_1 and D were expressed in international units and for vitamin G (riboflavin) in Sherman units from the beginning of the study.

FOOD FINDINGS

Calories.—The caloric allowance during pregnancy is an unsettled question. On account of the increased metabolic processes of pregnancy one would naturally expect an increased need, but the decreased activities of these women might indicate a lower allowance. Most authorities, however, state that 2,500 calories are the average allowance for pregnant women.[4, 5] According to the Report of the Technical Commission on Nutrition of the Health Organization of the League of Nations, requirements of pregnant women should be calculated as for normal adult women with an additional allowance for activity.

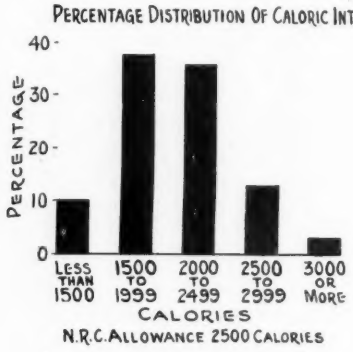


Fig. 5.

In our study of 514 food records most of the diets (83.9 per cent) ranged below 2,500 calories (Fig. 5). Two hundred and forty-two (47.1 per cent) had an intake below 2,000 calories; 189 (36.8 per cent), ranged between 2,000 to 2,499. Of the eighty-three women (16.1 per cent) whose diets produced 2,500 calories or above, 67 were between 2,500 and 2,999 calories, 14 between 3,000 and 3,499, and 2 had intakes above 3,500 calories. For the group as a whole the average intake was 2,013 calories; for the white women it was 2,034, and for negroes 1,953.

Protein.—Protein is constantly needed through life for its part in vital processes. Its importance during pregnancy and lactation should emphasized. The amino acids, derived from metabolism of proteins, are used in growth and tissue repair and after passing through the placenta by simple diffusion, are used by the fetus as available tissue-building material.[6] A sufficient protein intake in late pregnancy is believed to influence lactation with respect to quality and quantity of milk produced.

Restriction in protein intake in the pregnant woman lowers the nitrogen level, depletes body tissues and leads to nutritional edema. Anemia, poor muscle tone, lowered resistance, and insufficient lactation may also result from protein deficiency.

The protein allowance for the normal human adult has been set at 1 Gm. per kilogram of body weight.[4, 5] The protein intake recommended for the latter half of pregnancy is 1.5 Gm. per kilogram of body weight.[4] The National Research Council, in its recommended daily allowances for specific nutrients, states that 85 Gm. should be the daily intake for the average pregnant woman.

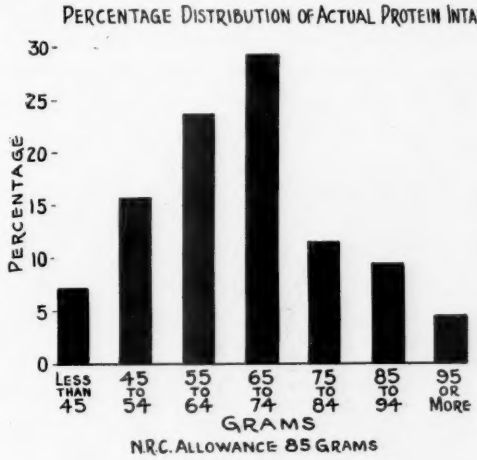


Fig. 6.

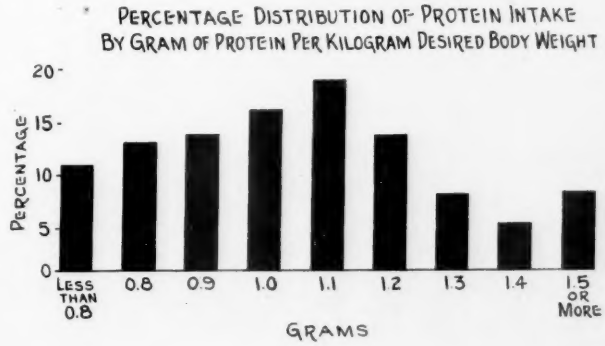


Fig. 7.

Most of the patients (86.9 per cent) in the group studied received less than 85 Gm. of proteins per day, the average was 66 Gm. (Fig. 6). When expressed in terms of desired body weight, 92.7 per cent of the series received less than the estimated requirement of 1.5 Gm. of proteins per kilogram (Fig. 7). The average was 1.1 Gm.*

*Desired body weight was based on height and weight tables for women of the U. S. Public Health Service. To this weight was added an allowance for the stage of pregnancy. A gain of 3 pounds per month was allowed each month after the third. The variations from desired weights are shown in Fig. 8.

Fats and Carbohydrates.—Fats and carbohydrates were regarded merely as sources of energy. If fat should provide 35 per cent of the calories in the human diets, then the diets studied went far above that figure. Ninety-one and four-tenths per cent of the women were consuming diets containing 35 per cent or more calories in the form of fat. The median intake of fat was 41 per cent fat calories. The median carbohydrate intake was 230 Gm.

Calcium and Phosphorus.—The skeletal development of the fetal body and maintenance of the integrity of maternal bony structure are more dependent upon calcium and phosphorus than upon any other inorganic substance. Experiments on domestic and laboratory animals have demonstrated that pregnancy and lactation create extra demands upon the calcium and phosphorus reserves of the mother. The utilization and absorption of calcium and phosphorus are determined by several factors. The most important are calcium-phosphorus ratio, amount of vitamin D available, quantity of fat available, and acid-base balance.[1, 7]

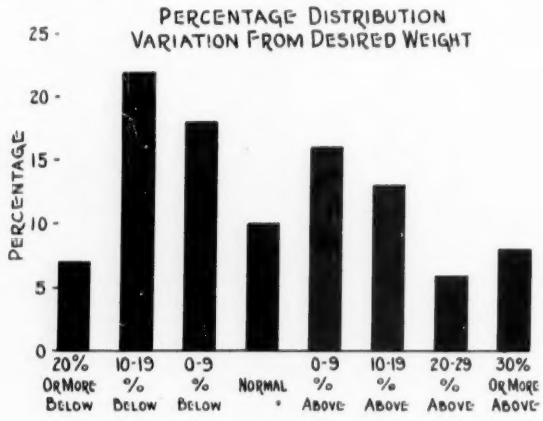


Fig. 8.

The requirement for calcium as recommended by the League of Nations is 0.75 Gm. daily for the normal adult. Pregnancy increases the need to 1.5 Gm. per day.[5]

Where a calcium adequacy exists in the diet, the presence of an adequate amount of phosphorus usually can be assumed. The phosphorus allowances of Stiebeling and Phipard[1] of 1.32 Gm. per day for all adults of 20 years and over may be accepted as reflecting approximately optimal nutrition of this element.

In our study we found only 15 patients (2.9 per cent) who had calcium intakes of 1.5 Gm. or more per day (Fig. 9). The average calcium intake was 0.7 Gm. The phosphorus intake was 1.3 Gm. or more per day in 369 (71.8 per cent); the average was 1.1 Gm.

Iron.—Iron participates in hemoglobin formation and consequently in the transportation of oxygen. The needs of the pregnant woman are accentuated by the demands of her growing organism, the developing fetus and the necessity for additional storage in the fetus.

The daily adult allowance of iron is believed to range from 12 to 15 mg.[8] Pregnancy increases the demand, and the allowances vary from

15[4] to 20 mg.[9] Only 30 women (5.8 per cent) had an intake of 15 mg. or more (Fig. 10), and the average intake was 10.3 mg.

Vitamin A.—The chief functions of vitamin A in human nutrition in the light of deficiency manifestations are: to maintain the integrity of epithelial tissues; to promote growth, fertility, and reproduction; to promote good tooth structure; to increase resistance to infections; and to regenerate visual purple.

The allowance of vitamin A is dependent upon the weight of the individual. The need in pregnancy is increased on account of accelerated metabolic activities of mother and growing fetus.

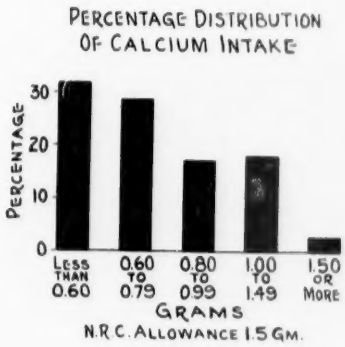


Fig. 9.

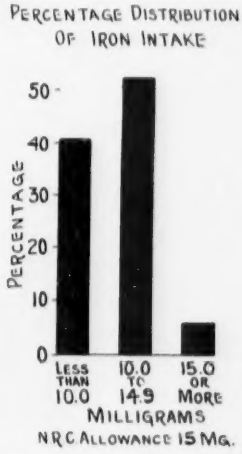


Fig. 10.

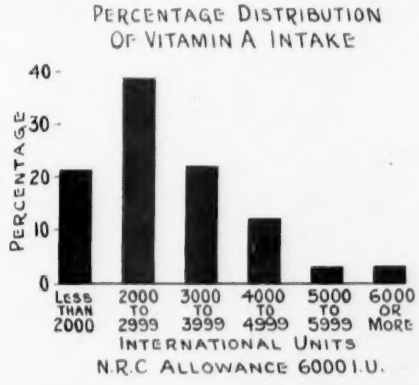


Fig. 11.

The allowance for adults, 20 years and over, has been given as 6,000 international units[1] and 5,000 international units.[5] The allowance for pregnancy has been stated by the National Research Council as 6,000 international units and by Stiebeling and Phipard[1] as 7,500 international units, while the League of Nations suggests 9,000 international units.

We found that only 18 (3.5 per cent) of the women in this series were receiving this much or more per day. In fact, the intake of more than half of the group was only 2,000 to 4,000 units (Fig. 11). The median was 2,700 units.

Vitamin B_1 (Thiamin).—It is generally accepted that vitamin B_1 plays an important role in the functioning of every cell rather than in the activity of a special organ or tissue system. Its storage is limited and daily replacements must be made. Deficiency in vitamin B_1 may lead to symptoms of varying degree, from the extreme clinical states such as beriberi, to the less well-defined syndrome of fatigue, loss of appetite, and other gastrointestinal symptoms, headache and mild neuritic symptoms.

The requirement of vitamin B_1 bears a distinct relationship both to caloric intake and body weight. Cowgill[10] estimated that the minimum requirement for a normal human adult is approximately 10 international units per 100 calories, or 300 to 350 units per day. This is equivalent to about 1 mg. of thiamin chloride. Increased requirements during pregnancy are conditioned principally by the demands of the fetus and the increased metabolism of the mother.

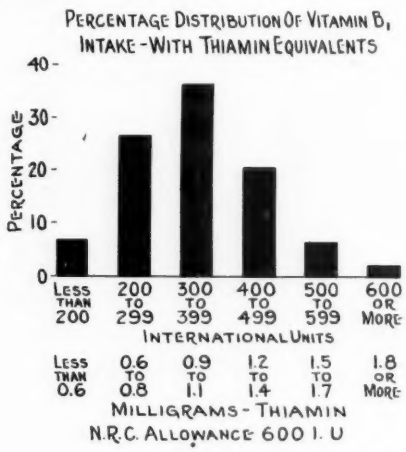


Fig. 12.

The League of Nations[4] suggested the daily pregnancy requirement of vitamin B_1 at 150 to 250 international units and the National Research Council[5] recommends 1.8 mg. thiamin chloride (approximately 600 international units vitamin B_1).

Our findings showed that only 9 women (1.8 per cent) received 600 or more international units a day (Fig. 12). More than half of the women had an intake of from 250 to 400 international units daily. The median was 340 units.

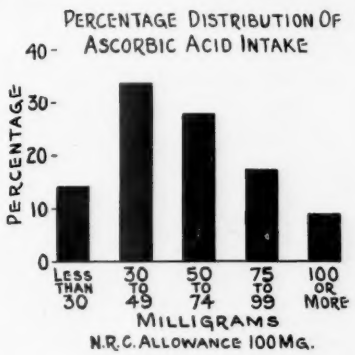
Vitamin C (Ascorbic Acid).—The most important function of vitamin C is to control the proper cementing of intercellular material. A deficiency is usually first manifested in tissues, such as teeth, bones, and cartilage, and a severe inadequacy gives rise to scurvy. Its role in combating infections cannot be overlooked. The need for vitamin C is increased during pregnancy on account of the parasitic action of the fetus.

Daily allowances of vitamin C have been recommended as 70 mg. for the moderately active adult woman by the National Research Council.[5] The allowance for the latter half of pregnancy is 100 mg. of ascorbic acid. The recommendation of the League of Nations[4] for this vitamin

is 870 to 1120 international units, or approximately 44 to 56 mg. of ascorbic acid.

In this series adequate vitamin C was furnished in the diets of only 45 patients (8.8 per cent) (Fig. 13). Over one-half received from 30 to 70 mg. of ascorbic acid. The median was 53 mg.

Vitamin G (Riboflavin).—Numerous physiologic roles have been attributed to vitamin G (riboflavin), but the one which has been agreed upon by most authorities is concerned with oxidation processes of the cell. Gross lack of vitamin G in the human being often accompanies other vitamin deficiencies and is characterized chiefly by lesions at the angles of the mouth, at the alae of the nose and on the ears. Because riboflavin acts in part as an enzyme concerned with the metabolism of carbohydrates its allowance has been based on caloric intake.



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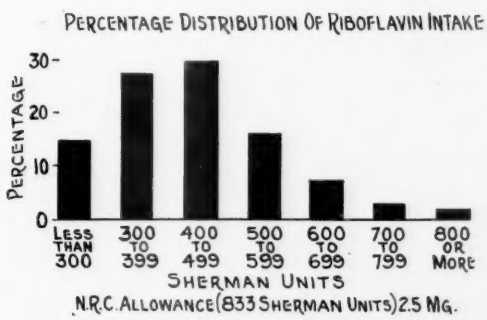

Fig. 14.

The National Research Council[5] has set the allowance for a moderately active, 70 kilogram man, consuming 3,000 calories daily, at 2.7 mg. For pregnant women, these authorities have defined an allowance of 2.5 mg., presuming that there is an intake of 2,500 calories. Stiebeling and Phipard,[1] although they state no recommendation for pregnancy, suggest 1.8 mg. of riboflavin (600 Sherman units) as the daily allowance for an adult of 20 years or over.

We compared the vitamin G (riboflavin) intake of the group with the Council allowance of 2.5 mg. (approximately 833 Sherman units), and found that only 8 women (1.6 per cent) were receiving that much (Fig. 14). Over one-half of the group were consuming 300 to 500

Sherman units (approximately 0.9 to 1.5 mg. of riboflavin). The average was 420 Sherman units (1.3 mg.).

Vitamin D.—Vitamin D is necessary for the proper formation of bones and teeth by reason of its regulation of calcium and phosphorus utilization. Vitamin D deficiency contributes to the rickets of early childhood. The prematurely born baby requires twice the amount of vitamin D as a full-term baby to prevent the development of rickets.[11] From this fact it appears that the need of the woman in late pregnancy is increased.

There is lack of agreement as to the requirement of this vitamin for all age groups, except infancy and very young children, although the League of Nations[4] recommended 340 international units of vitamin D daily for pregnant and lactating women. To protect a pregnant woman against any possible vitamin D inadequacy, Park[12] suggests an intake of 800 international units daily. The Council recommends 400 to 800 units.

It is not possible to measure the amount of vitamin D received by the women of this group, because the amount of sunshine they received was a variable and unmeasurable quantity. According to the few available vitamin D values for foods, these women received amounts varying from none to 140 international units daily. The frequent use of vitamin D concentrates in all classes of pregnant women insures for a certain proportion a sufficient amount of this factor.

ECONOMIC STATUS AND CORRELATIONS

As previously stated, the economic status of these women was classified by the weekly per capita income, and the totals in each group were given.

Stiebeling and Phipard[1] found that certain trends in consumption of different food factors were apparent when correlated with the economic status. They noted a definite increase in the intake of calories, protein calcium, iron, vitamins A, B, and G, and nicotinic acid among the white families in the North Atlantic Cities.

McCance, Widdowson and Vernon-Roe,[13] in their study of the diets of pregnant women in England, found that at different economic levels the intake of calories, fat, and carbohydrate was little affected by income. The intake of protein, calcium, phosphorus, iron, and vitamin B rose steadily with increased income.

Our findings, after correlating certain food factors with economic status, are discussed in the following paragraphs (Fig. 15).

Because a large proportion (82 per cent) of the negro women were in the lowest economic group, we did not find it feasible to make any correlations with income.

The average energy intake among the negroes was 1,953 calories. In the white women the average caloric intake was greater in the highest income group than in the lowest income group. The rise, however, was not steady and, therefore, not significant.

The average protein intake in the negro group was 70 Gm. Among the white women of the lowest income group the average protein intake

was 64 Gm. There was a steady rise to the highest income group whose average was 69 Gm.

The intake of carbohydrate and of fat was not affected by income.

Calcium intake, when correlated with economic status, showed an increase among the white women from lowest to highest income groups from 0.7 to 0.9 Gm. The average intake of calcium among the negroes, 0.6 Gm., was lower than that of the economically lowest white group.

There was a slight rise in iron intake with increasing income. The average for all groups was approximately 10 mg.

In the white group vitamin A intake rose from a median of 2,500 international units in the lowest to 3,000 units in the uppermost economic bracket. The negro group had a median intake of 2,600 units.

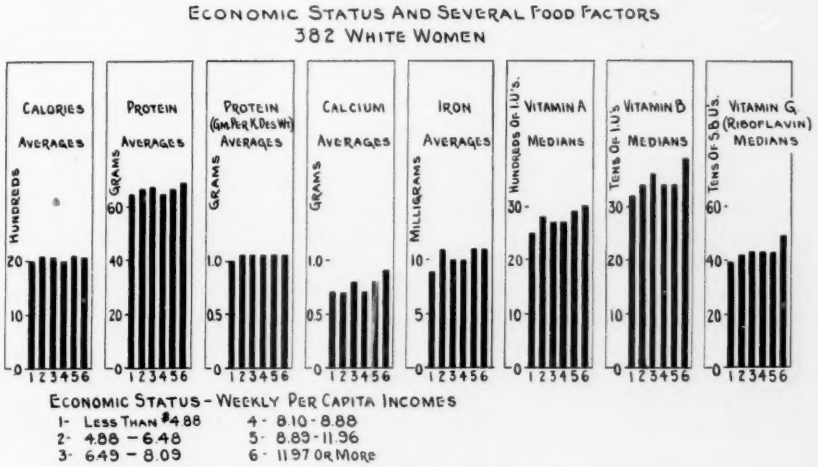

Fig. 15.

The intake of vitamin B_1 in the white women increased from 320 international units in the lowest group to 390 units in the highest. The median for the negro group was 320 units.

The intake of ascorbic acid rose from 46 mg. in the lowest group to 78 mg. in the highest. The median for the negroes was 41 mg.

The intake of vitamin G (riboflavin) definitely followed the increase in income in white women from 390 Sherman units in lowest group to 490 in the highest. The median for the negroes was 400 units.

COMPLICATIONS OF PREGNANCY

To determine the influence of nutritional deficiencies on some complications of pregnancy and childbirth, we have made certain correlations.

In the group with no complications of pregnancy, 392 women, the median intake of protein was 66 Gm.; in the group with various complications, including toxemia, the median intake was 65 Gm.

TOXEMIA

In view of the fact that protein deficiencies have been regarded by some as a possible etiologic factor in toxemias of pregnancy through their influence on protein metabolism, or on serum proteins, we have correlated protein intake with the presence of toxemia. There were 60 cases of toxemia of late pregnancy: 46 were mild pre-eclampsia, 6 were severe pre-eclampsia, and 8 were hypertensive cardiovascular disease. The median protein intake for this group of toxemias was 67 Gm. Since in the normal group we found protein intakes as low as 30 Gm., and since in the toxemia group the most severe cases did not show the lowest protein intake, our findings do not bear out the above-mentioned theory. Comparing the normal and toxemic groups on the basis of grams of protein per kilogram of desired body weight, we found the same lack of positive correlation, and this held true also for vitamins A and B, the other food factors correlated.

There were too few cases of abortion and hemorrhage, pyelitis, and cystitis, and intercurrent infections to warrant definite conclusions.

In cases which presented a history of nausea and vomiting in early months of pregnancy, or who complained of numbness, fatigue and muscle spasm during the latter months of pregnancy, there was an average intake of 400 international units of vitamin B_1, while 84 per cent of this group had an intake below the pregnancy standard of 600 units of vitamin B_1.

PREMATURITY

In the 502 cases for which delivery records were available, 29 children weighing less than 2,500 Gm. each were born singly, and 3 sets of twins had birth weights below this level. Eighteen of the premature births could be explained by obstetric or medical complications, such as syphilis, toxemia, and rheumatic heart disease. One premature twin delivery could be explained by premature separation of the placenta. In the 11 cases in which no explanation could be found for the single premature birth, the average protein intake was 63.6 Gm. In the 2 sets of twins, where no cause other than the multiple pregnancy existed, the maternal intake of protein was 60 and 61 Gm., respectively. If one compares these figures with the average protein intake of the entire group, which was 66 Gm., it is hardly likely, concluding from this small series, that protein deficiency plays a part in the production of premature labor.

We were not able to prove any relationship between prematurity and vitamin A deficiency, since the median intake for the mothers of premature babies was 3,100 international units, slightly higher than the median for the entire series.

STILLBIRTHS

Four of the pregnancies in this series terminated in stillborn fetuses. All could be explained by obstetric complications.

NEONATAL DEATHS

Fourteen neonatal deaths occurred in the series. The weights of the babies ranged from 500 to 3,500 Gm. Ten of the 14 weighed less than

2,500 Gm. Obstetric factors, such as birth injury, toxemia, premature separation of the placenta, monstrosity, myoma, and pelvic infection accounted for 10, heart disease and syphilis for two, while two others were unexplained. In the 2 cases where no medical or obstetric factor could be found to explain the premature delivery and neonatal death, the diets of the mothers were markedly deficient. These two instances, however, do not warrant any conclusion as to a relationship between neonatal death and poor eating habits.

WEIGHT OF INFANTS

No correlation could be obtained between the weight of the infant and dietary intake. We are inclined to agree with Adair[14] who says, "the birth weight does not seem to be materially increased by abundant nutriment nor is the reduction significant except in actual maternal deficiency diets."

MORBIDITY

Seventy-one women were morbid after delivery. An analysis of the diets of these women showed that in protein and vitamin A and C intake they were not markedly different from the remainder of the group.

LACTATION

The storage of nitrogen in the latter part of pregnancy is essential for adequate lactation, according to Coons and Blunt,[15] and a sufficient intake of protein is necessary to insure such storage. We wanted to know whether those women who were able to nurse their babies had a higher protein intake than those who did not. The 339 who nursed their babies, the 85 whose babies were formula fed, and the 59 whose babies had supplementary feedings, all showed practically similar protein intake. There was a slight increase in the protein intake of the mothers whose babies were formula fed, and the data were investigated for possible relationship between lactation and economic status, but no definite conclusions were reached.

NORMAL GROUP

It was felt desirable to evaluate the food intake of those women who experienced an apparently normal reproductive process and to compare it with the whole series. The selection of this group depended upon several factors: normal pregnancy with no major complications, normal, spontaneous delivery, prophylactic low forceps, or manual assistance in a breech, and a normal child weighing from 2,500 to 4,500 Gm., which was breast fed during the hospital stay. Two hundred and fifty women comprised this group. When we compared their dietary adequacy with that of the entire 514 women, we found no variation in the intake of protein, calories, calcium, iron, vitamins A, B_1, C, and G. The mere fact that a group of women on a diet well below the recommended allowances for good nutrition bore normal children after an apparently normal pregnancy and were able to nurse them during a short observation period does not signify that the standards are being set too high. Rather, let us presume that this is another instance of compensation by nature in its effort to produce living offspring. Only a long-range study could determine the ultimate effect of a poor diet upon both mother and child.

DISCUSSION

Our analysis of diets consumed by 514 women in the maternity services of three Philadelphia hospitals shows that errors in food habits, and inadequate diets were the rule (Fig. 16). This could be attributed

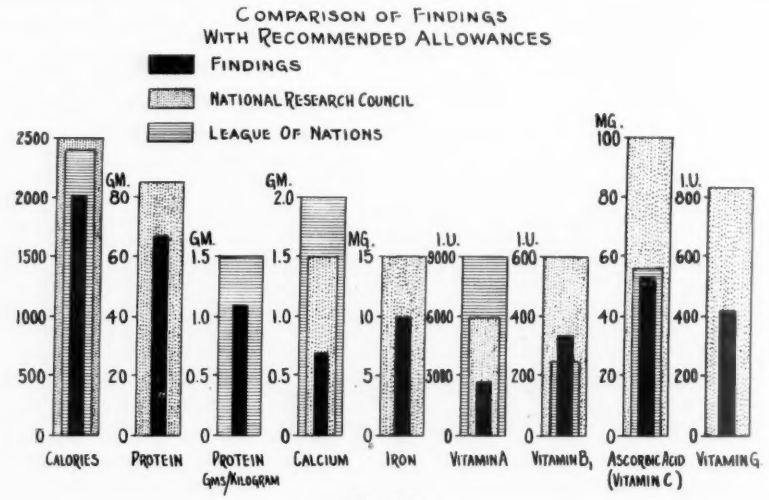

Fig. 16.

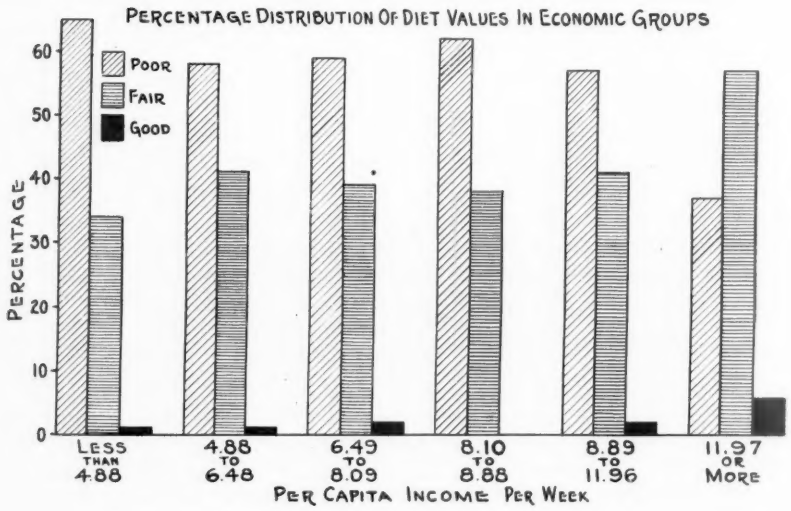

Fig. 17.

in many instances to poor economic circumstances, but often where the income was not low, a lack of knowledge or a disregard of values was responsible for poor diets.

When we applied the yardstick of nutrition of the National Research Council to the assembled data, we found only 10 diets (approximately 2 per cent) met all the requirements and could be termed good (Fig. 17).

A fair diet, between optimal and minimal standards, was found in 209 instances (41 per cent) (Fig. 18). The remainder, 295 (57 per cent) diets, were below the minimal requirements in sufficient number of items that we classed them as poor (Fig. 19). Where one item alone was markedly out of line, calcium deficiency was the most frequently encountered. In establishing a set of minimum standards from the yardstick of nutrition of the Council we followed a procedure previously used by Stiebeling and Phipard.[1] Thus the allowances for vitamins were reduced 50 per cent, and for protein and minerals 33 per cent.

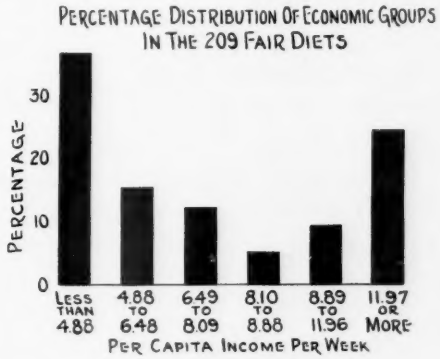

Fig. 18.

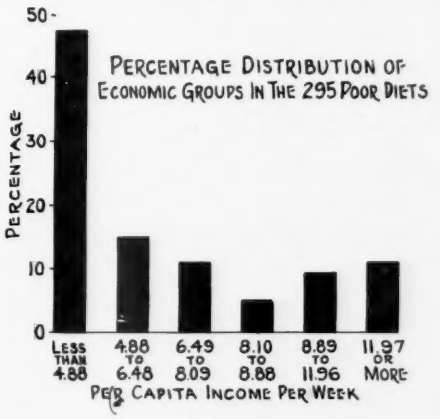

Fig. 19.

Similar instances of bad dietary habits during pregnancy have been noted by other observers.

Burke[16] found only one-fifth of the prenatal cases she studied in Boston met the optimal requirements for calcium, and not one case had an excellent protein intake. Teel[17] found more than one-half of the dietary histories of a small group in Boston deficient in vitamin C. Tompkins[18] observed in Philadelphia an average intake of only 50 Gm. of protein in a group of several hundred prenatal cases. This low protein intake was associated with an excess intake of carbohydrate.

In a study of the diets of mothers of congenitally deformed children in Philadelphia, Murphy and Bowes[19] found marked deficiencies in protective foods. In Maryland, Leamy[20] noted that 40 per cent of a group of prenatal cases at one county clinic had an intake of less than 1,000 calories a day, and that only 4 per cent had enough iron in the diet. From another district in Maryland, Whitsitt[21] states that over 20 per cent of the prenatal cases showed from borderline to frank anemia on a food intake in which the main articles were hog meat, white bread, potatoes, corn syrup, cabbage, and dried beans. Milk, butter, eggs, green vegetables, and fruit were notably absent. Ross and his co-workers[22] refer to an equally unbalanced, typically pellagra-producing diet common among pregnant women in some districts of North Carolina. McCance and others[13] in England, noted a deficiency in minerals and in total calories in the diets of pregnant women at various economic levels. Ebbs,[23] of Toronto, found that over one-half of a group of 400 pregnant women were consuming diets which he classified as poor.

Such evidence points to a wide prevalence of dietary deficiency among pregnant women. It has recently been announced that the physical examinations of the first million men conducted under Selective Service caused 133,000 to be rejected as unfit for military service from disabilities directly or indirectly connected with nutrition. If a certain percentage of such disabilities in the inductees could be attributed to malnutrition, and we could assume its incipiency in poor prenatal nutrition, then it behooves us to improve the nutritional status of the next generation.

Education and improvement of economic status are important factors in improving the situation of widespread dietary deficiency in pregnancy. The question of increased income is a problem we do not feel relevant to this paper. We feel assured that through the agency of the Surplus Marketing Administration with its Stamp Plan for the distribution of certain protective foods, and its school luncheon program much good is being accomplished. Particularly, is this true among the twenty million of our population on relief whose average meal, September, 1940, cost five cents, and whose average weekly food expenditure was one dollar.

In the employed wage earner group the entire family and the size of the food budget must be considered carefully in providing an adequate diet for pregnant mothers without depriving the other members. Simple and low cost diets may be arranged which provide adequate intake in practically all nutritive factors. The Children's Bureau by means of poster and pamphlet, "Prenatal Care," have described two such diets. An analysis of these diets shows their content (Table II).

The factor of education is a paramount one in the population as a whole. The problem as it affects us as obstetricians may be summed up in a statement by Burke:[16] "There is no period in life (the prenatal period) where effective and intelligent nutrition teaching would result in greater gains to national health. The reason for this is threefold: first, it would result in improved maternal health and lowered maternal

TABLE II

	CHILDREN'S BUREAU POSTER	"PRENATAL CARE" PAMPHLET	NATIONAL RESEARCH COUNCIL
Protein (Gm.)	92	95	85
Calories	2,614	2,559	2,500
Calcium (Gm.)	1.5	1.6	1.5
Iron (mg.)	16	20	15
Vitamin A (I.U.)	5,785	8,675	6,000
Vitamin B_1 (I.U.)	500	492	600
Ascorbic acid (mg.)	59	71	100
Vitamin D (I.U.)	84	130	400-800
Riboflavin (mg.)	1.9	2.3	2.5

mortality; second, it would bring about marked improvement in child health and development; third, it would also bring about improved nutrition of the family as a whole."

Research is needed in this problem for more accurate determination of the optimum and minimum requirements of the food factors as well as the conditions which modify their absorption and utilization in pregnancy and lactation. Long term studies with adequate parallel control groups will be necessary to determine the ultimate results in both mother and child. In this respect we realize the limitations of a short run study which we present.

To promote a general improvement of maternal welfare, medical groups must support and continue to support the national nutrition programs now being outlined and instituted. They should lead in individual investigations and more detailed studies in their own areas.

SUMMARY

1. The diets of 514 pregnant women were analyzed with the result that only 10 could be termed good, 209 fair, and 295 poor. They fell much below the standard in all elements when compared with the recommended dietary allowances of the National Research Council.

2. Caloric, carbohydrate, and fat intake were found to be unaffected by income. The intake of vitamin A, vitamin B_1, ascorbic acid, and riboflavin rose with the income. Protein, calcium, and iron showed a slight rise with increased income.

3. This small series did not show any positive relationship between dietary adequacy and the occurrence of certain complications of pregnancy and childbirth. (a) There was no evidence that toxemia occurs in the presence of insufficient protein, vitamin A or vitamin B_1 intake. (b) There were not enough cases of abortion, hemorrhage, pyelitis and cystitis, and intercurrent infections to justify any conclusions. (c) Protein deficiency did not seem responsible for the production of premature labor in a short series of cases. The same may be said for vitamin A. (d) The number of neonatal deaths and stillbirths was too

small to show any positive relationship to dietary inadequacy. (e) The diets of those women who were morbid after delivery did not differ markedly from the remainder of the group with respect to protein, vitamin A, or vitamin C intake. (f) Protein intake apparently had no bearing on the ability of the women to nurse their babies during the hospital stay.

4. Eighty-four per cent of a group who presented a history of nausea and vomiting in early pregnancy had an intake below the pregnancy standard of 600 units of vitamin B_1.

5. Two hundred and fifty women in the series experienced an apparently normal reproductive process. Their food intake showed no variation from that of the entire group of 514.

We are grateful to Mrs. Anna DePlanter Bowes, Dr. Pauline Beery Mack, Dr. R. P. Custer, and Dr. E. D. Burdick for their valued technical assistance, to Dr. F. A. Miller and to Dr. B. Hark for clinical material, and to the social service staffs of the three hospitals where the study was conducted, for their cooperation.

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A CLINICAL EVALUATION OF FETAL ELECTROCARDIOGRAPHY

A Study of 100 Cases by a New Technique and an Improved Instrument

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THE recording of fetal heart beats by electrocardiography, while devoid of diagnostic significance with regard to intrinsic cardiac lesions in the fetus, is fast becoming a useful procedure in obstetrics. The technique and instruments employed in this study and our uniform success in obtaining clear records of fetal heart action seem to warrant the addition of this test to the obstetric diagnostic armamentarium. The description of a new technique, by which many previous pitfalls and difficulties are avoided, warrants publication. This study of 100 consecutive, full-term pregnancies terminating in natural labor, yields a normal fetal electrocardiographic standard that is of value to the obstetrician. Many of the obstetric abnormalities encountered are briefly mentioned but no statistical use has been made of this material.

Cremer,[1] in 1906, successfully accomplished fetal electrocardiography when the electrocardiograph was new. His accurate records of the fetal heart in utero showed promise of a new diagnostic aid in obstetrics. Cremer's achievement was followed by a long period during which investigators failed to obtain satisfactory fetal electrocardiograms; and not until 1930, when Maekawa and Toyoshima[2] took advantage of improvements in electrocardiographic instruments, did the subject become really ripe for further study. In the past ten years numerous records of the fetal heart have been published and various techniques have been outlined.

The technical difficulties involved have been of two kinds: namely, the limitations of the electrocardiograph, and the limitations of the subject. The instrument used was formerly cumbersome, and not sufficiently sensitive to record satisfactory fetal curves. In 1925, the first portable machine was manufactured;[3] and in 1932, an improved electrocardiograph[4] combining light weight, increased sensitivity, and accurate performance was introduced by one of us. This instrument has been developed into the commonly used "Cardiette," an amplifier type of instrument, which has found general acceptance. For the special purpose of this study, the makers of the "Cardiette" have furnished us with an unusually sensitive, improved instrument, which, without sacrificing accuracy and portability, is capable of deflections up to 6 cm. per millivolt, approximately six times the standard sensitivity of the old

string galvanometer. Without such increased sensitivity fetal deflections are so small as to be almost imperceptible. With this instrument, the use of a pre-amplifier or any additional amplifying device is unnecessary.

The limitations of the subject have presented a difficult problem to investigators. The fetus, not directly accessible for electrocardiographic study, is enclosed within the maternal body and cannot be isolated from electrical effects produced by the maternal heart, respiratory muscles, skeletal muscles, etc. The use of an electrode applied to the cervix through the vagina, or of a rectal electrode, presents obvious disadvantages, and can scarcely be developed into a useful routine procedure. Employment of the standard limb leads of the mother has several disadvantages. Elaborate precautions must be taken to secure relaxation and minimize muscle tremor. With increased instrumental

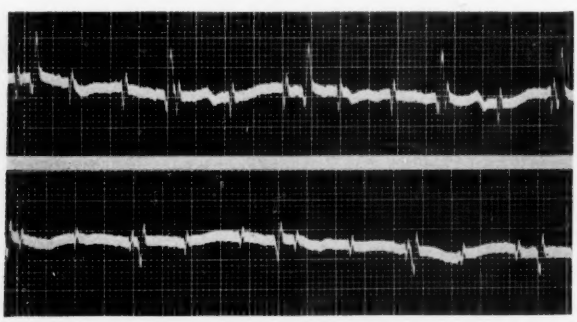

Fig. 1.—Fetal electrocardiograms recorded by the improved method, five days before delivery. The maternal rate is approximately 64 and the fetal rate 155. The upper curve was recorded with electrodes in the second position and the lower curve with the electrodes in the third position. Standardization is 6 cm. per millivolt. Time is in fifths and twenty-fifths of a second.

sensitivity, slight muscle tremors, imperceptible, in the standard electrocardiogram, become evident and impair the record. In addition, the maternal electrocardiogram becomes so enlarged that the smaller fetal deflections are overshadowed and difficult to observe. Most of these difficulties have been overcome by applying electrodes directly to the abdomen of the mother. With the technique to be described, no prolonged period of rest or relaxation is necessary. Tremors due to skeletal muscle are generally absent. The maternal electrocardiogram is so reduced in size that even with maximum instrumental sensitivity, it does not overshadow the fetal deflections. The method presents no complications or difficulties, and offers no possible danger to mother or child. It is eminently suitable as a routine method of fetal electrocardiography, its superiority to other methods being demonstrated by our success in recording fetal curves, not merely during the last forty days before delivery, but as early as the fourth month of gestation. The clarity with which fetal electrocardiograms may be recorded by our method is illustrated in Fig. 1.

TECHNIQUE

This method, developed by Mann,[5] is carried out as follows: The patient reclines comfortably on an examining table, couch, or bed, either flat or with the head slightly elevated. Smoking, gum chewing, talking, and other nervous stimulation, such as the presence of observers, strong lights, loud sounds, etc., should be eliminated. Corsets or heavy girdles should be removed but light elastic underwear does not interfere and, in fact, may help to hold one electrode in place.

The lower abdomen is exposed and standard electrocardiograph electrodes are applied after rubbing the skin with the usual electrode paste. These electrodes are applied in succession in the following six positions:

The electrodes are covered with a towel or sheet and their position is maintained by the patient's hands, which rest lightly on the sheet. The lower electrode, which is placed below the umbilical level, can often be kept in place by elastic underwear. The right arm wire of the electrocardiograph is connected only to the upper electrode in positions *a, b, c,* and to the right electrode only, in positions *d, e, f.* The left arm wire is connected to the other electrode. The instrument is set on Lead I and about thirty maternal deflections are recorded, the first 15 with a sensitivity of 3 cm. per millivolt, and the remaining 15 with a sensitivity of 6 cm. per millivolt. These 30 beats are recorded continuously without stopping the camera, the change in sensitivity being accomplished by simply advancing the sensitivity control to its maximum position after half the record has been taken. Standard millivolt deflections are recorded in the customary manner. In the sixth or last record, it has also been our custom to introduce a signal at five-second intervals, measured with a stop watch, in order to check on the accuracy of the time markings. Occasionally, with rapid maternal heart rates, it may be advisable to record more than 30 beats; and conversely, if the rate is very slow, fewer than 30 beats may be recorded. However, generally, 30 beats will provide a long enough record to enable the fetal deflections to be counted for twenty seconds, so that the fetal rate can be determined with reasonable accuracy. Occasionally, a very nervous or apprehensive patient may be unable to relax and the record may be technically unsatisfactory. In such cases, it has been our custom to proceed exactly as usual with the recording. Upon the patient's next visit, the electrocardiogram is repeated and the patient, having become more familiar with the routine, is invariably more cooperative. An occasional patient may display constant tremor of the large muscles, unusually deep respiration or a persistently rapid heart rate in spite of manifest mental and physical relaxation. In only 2 of the 100 patients did these syndromes frustrate our efforts; in one case there was a muscular tremor with tachycardia, and in the other, a somatic tremor with deep respiration. One of these patients was cardiographed only once and the other only twice, and had greater persistence been employed, final success could have undoubtedly been achieved.

CLINICAL STUDIES

The material for study consisted of successive, unselected patients attending the prenatal clinic. Each patient was cardiographed. As a rule, they did not present themselves until the fifth or sixth month of gestation, but 13 patients were seen before the fifth month. They were

observed in the clinic until parturition; 90 of the birth records were obtained from our own obstetric department and 10 from the other institutions where the labors took place. All premature, abnormal and cesarean section deliveries were excluded. Only full-term patients with

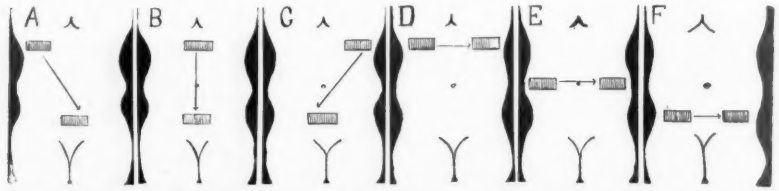

Fig. 2.—The six electrode positions as applied in succession in the new technique. *A*, *B*, and *C* are longitudinal and *D*, *E*, and *F* are transverse. Electrodes are covered with a towel or sheet.

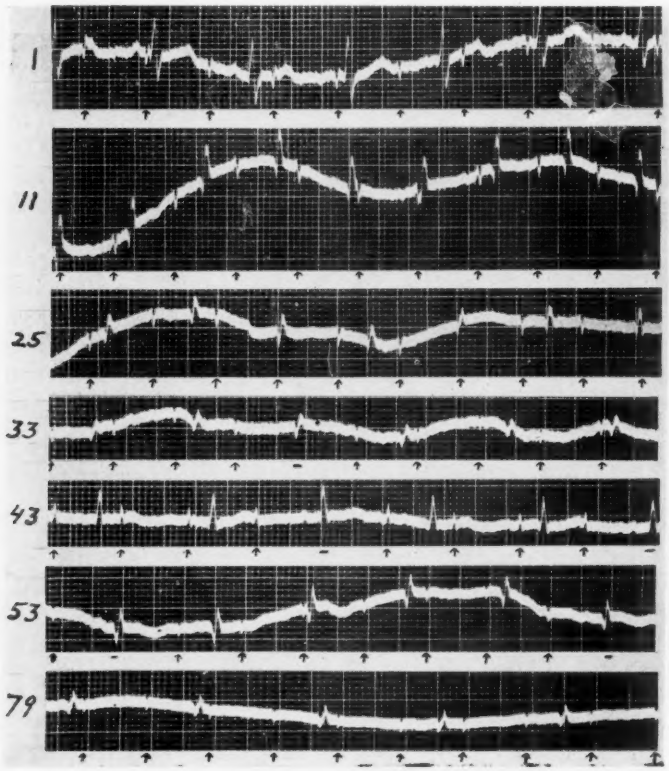

Fig. 3.—Electrocardiograms obtained during the last eighty days of pregnancy. Numerals at left indicate the number of days before delivery when the graph was taken. Maternal deflections are large and slow, widely spaced. Fetal deflections, indicated by arrows, are smaller and more rapid. Standardization is 6 cm. per millivolt.

spontaneous labors, who delivered normal babies, were taken into account. Thus, our electrocardiograms were obtained at accurately determined time intervals before labor. The records and tables, compiled from this unselected group of normal gravidities, therefore, may be offered as an acceptable standard for normal fetal electrocardiography.

Sixty-eight of the women in this series were negroes and 31 were white. (One negro woman was electrocardiographed throughout two consecutive pregnancies.) The ages ranged from sixteen to forty with an average age of about twenty-six years. There were 32 first pregnancies, 29 second, 13 third, 14 fourth, 4 fifth, 5 sixth, and one instance each of seventh, eighth, and tenth pregnancies.

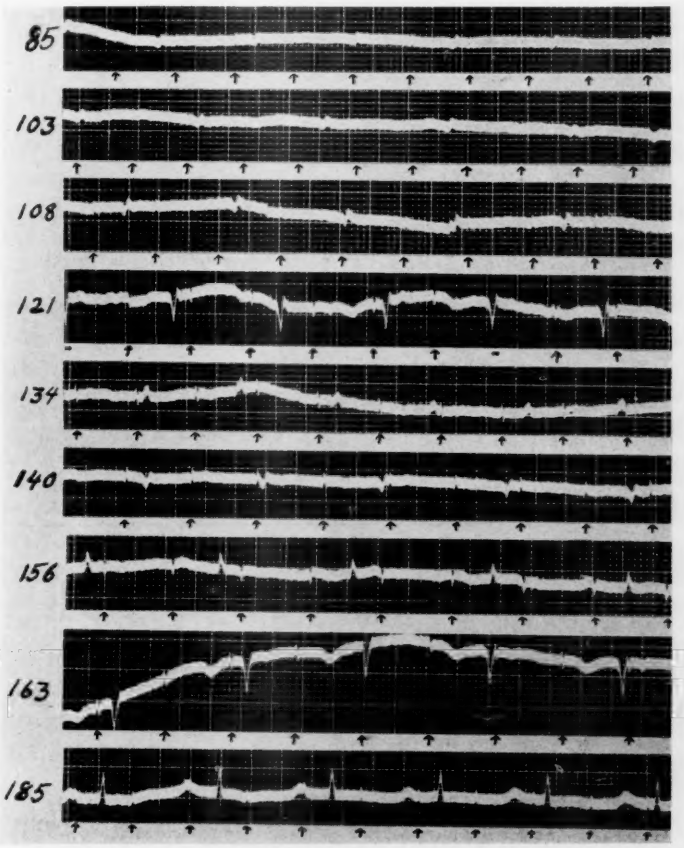

Fig. 4.—Electrocardiograms obtained between the eighty-fifth and one hundred and eighty-fifth day before delivery. The lowermost curve was the earliest obtained, 185 days before delivery. This pregnancy is not admitted to this series, since it was terminated by cesarean section, one day after the inception of labor. Standardization is 6 cm. per millivolt.

Fifty-five male children and 45 female children were delivered. Eighty-two instances of left occipitoanterior position, 14 of right occipitoanterior, and four breech presentations are tabulated from the records. All the mothers and children left the hospital in good health.

Of our 100 patients, only two failed to exhibit a satisfactory fetal curve at some time during pregnancy; one of these was cardiographed only once and the other twice. Both these patients showed marked muscle tremor; in addition one showed unusually deep respiratory excursions and the other had a sinus tachycardia with a rate of about 124. A total of 153 electrocardiograms were taken, the maximum number of records of any patient being 4.

Of these records, 116 (75.8 per cent) showed definite fetal deflections sufficiently clear to permit accurate determination of the fetal heart rate. Thirty-seven (24.2 per cent) did not show satisfactory fetal deflections and were considered negative. Ninety-eight of the 100 patients showed one or more satisfactory fetal curves. Figs. 2 and 3 illustrate typical curves obtained in the last seven lunar months of pregnancy.

The earliest electrocardiograms, four in number, taken in the third lunar month, were all negative. Of 9 records taken in the fourth lunar month, 11 (61 per cent) of 18 records showed definite fetal deflections. In the sixth lunar month, 28 out of 29 (96.5 per cent) curves were satisfactory. In the seventh, the proportion of positive curves decreased somewhat, namely, 14 out of 19 (73.7 per cent); in the eighth month, only 14 out of 26 (53.8 per cent) tests were positive. This sharp drop arouses some speculation as to its cause. In the ninth and tenth lunar months, the high proportion of positive curves reappeared, –26 (96.3 per cent) of 27 graphs and 20 (95.2 per cent) out of 21 graphs, respectively. These findings are presented in Table I.

TABLE I. SHOWING RESULTS OF ELECTROCARDIOGRAPHY FROM THIRD TO TENTH LUNAR MONTHS

LUNAR MONTH	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH
Total records taken	4	9	18	29	19	26	27	21
Positive fetal E.C.G.	0	3	11	28	14	14	26	20
Negative fetal E.C.G.	4	6	7	1	5	12	1	1
Per cent positive	0	33	61	96.5	73.7	53.8	96.3	95.2

DISCUSSION

It is interesting that previous investigators in this field report successful fetal records only in the ninth and tenth lunar months. The progressive decline of successful results from 96.5 per cent in the sixth month to 73.7 per cent in the seventh month and to 53.8 per cent in the eighth month is difficult to explain, whereas, in retrospect, the sudden drop from the high percentages in the tenth and ninth months to the low value in the eighth month might lead one to believe that successful electrocardiograms would be increasingly more difficult to obtain in patients during the early months of pregnancy. That this is incorrect is clearly shown by the high percentages observed during the months of the previous trimester. However, tests during the first trimester of pregnancy show a definitely low percentage of successful electrocardiograms (no readings obtained in the third month) in spite of our attempts to obtain these early records with the new instrument and improved technique. We reasonably conclude, therefore, that, under the present new technique, electrocardiography after the fourth lunar month of pregnancy is practicable.

Table I shows that of the 101 records from the fourth month to the eighth month inclusive, 70, or 69.3 per cent, showed positive fetal curves, and during the last two lunar months, 46 out of 48 results were successful, a percentage of 96. During the entire interval from the fourth to

the tenth lunar months, the percentage of success is 77.86 per cent. Thus, the high incidence (96 per cent) of success in the last two lunar months, and, indeed, the fairly high percentage (77.9 per cent) of visible fetal curves obtained during the entire interval, namely, from the fourth to the tenth lunar months, inclusive, would seem to warrant the use of electrocardiography in obstetric work.

The reason why fetal electrocardiograms are not as readily obtainable in certain months, offers interesting material for speculation. Failure to obtain fetal curves during the third lunar month is understandable when one considers the small size of the early fetal heart, and the fact that the fundus at this stage of development is not in contact with the anterior abdominal wall. During the fourth lunar month of gestation, the fetal heart approaches the size of 1 cm. and the surrounding uterine fundus begins to project above the bony pelvis and is at the same time in more constant contact with the anterior abdominal wall. Thus, better contact with the abdominal wall as well as fetal growth, account for the higher percentage of clear fetal heart curves,

It follows also that with the continued increase, month by month, in the size of the fetus and the uterus, a progressively higher degree of successful electrocardiograms should be obtained. We are at a loss, however, to explain the spectacular decrease in the eighth month to a 53.8 per cent incidence. The explanatory conjecture, that during this month a relative or sudden increase in amniotic fluid might insulate the fetus and "short circuit" its electrical output, would seem inadequate, since several electrocardiograms taken in a case of fetal gastroschisis with a 3,000 c.c. hydramnios were indisputably clear and successful. On the contrary, however, in another instance of hydramnios (with twins), the fetal heart rate was unobtainable by electrocardiography during the eighth month of pregnancy. Notwithstanding the former instance, our general experiences would lead us to believe that a fetus close to the abdominal wall presents the optimum condition for successful electrocardiography.

This study permits us to investigate statistically the question of relationship between the fetal heart rate and sex. The average heart rate of the 55 male fetuses recorded in our series was 148.7 beats per minute; and the average rate of the 43 female fetuses was exactly the same. Evidently, an averaging of fetal heart rates gives no indication of the sex of the child. In order to break these figures down for a more detailed analysis, a chart was constructed (Fig. 5). In this chart, male and female, negro and white children are designated by symbolically marked black and white circles, indicating the respective heart rates and time in days before delivery, at which the record was taken. No tendency toward correlation between rate, sex, or color is observed. It seems logical to conclude, therefore, that the fetal heart rate offers no evidence as to the sex of the child.

A study of Fig. 5 does, however, give us some interesting information about the relation of the fetal heart to the duration of pregnancy. The simple average fetal rate in the last six lunar months of pregnancy declines gradually from a maximum of about 165 beats per minute in the fourth month to about 138 in the eighth lunar month, following which there is a rise of a few points in the last two months of pregnancy. This is also indicated in the chart by the broad line, which delineates weighted average rate. It is obvious from a glance at the chart that the spread or individual variation from this average is wide and that conclusions drawn from the average rate should be applied to the individual heart with caution.

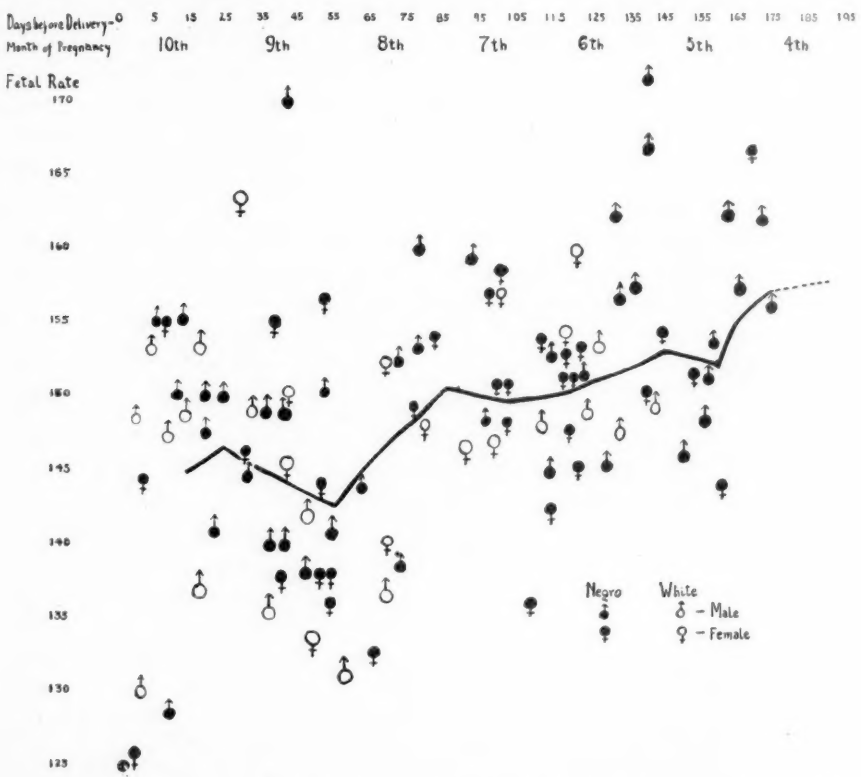

Fig. 5.—Recording of negro and white fetal heart rates in both males and females in the last six and one-half months of pregnancy. The weighted average line indicates a definite and slowly progressive decrease in the fetal heart rate as delivery date is approached. The fetal rate bears no relationship to sex or color.

The question of the relationship between fetal and maternal heart rates may also be subjected to statistical study. The impression that the fetal and maternal rates generally bear some simple ratio or mathematical relation to each other, is not substantiated. This is demonstrated in Fig. 6.

Fig. 6 illustrates graphically the various maternal and fetal rates in our series. Each line represents a single, synchronous determination of a fetal and maternal heart rate. The upper end of the line indicates the fetal heart rate; and the lower end of the line indicates the maternal

rate. The length of the line, therefore, indicates the difference in rate between fetal and maternal hearts. Our chart shows that there is no constant difference in rate between fetal and maternal heart rates, that rapid fetal rates are not indicative of slow maternal rates. Inspection of the chart will show that there is no tendency toward any constant ratio or correlation between fetal and maternal rates.

Abnormal conditions in the mother or fetus were encountered during this investigation. Such cases are not included in the preceding charts and tables but are here reported separately.

Cesarean operation was performed in five instances. These patients all showed positive fetal electrocardiograms. Pseudocyesis at the menopause simulated pregnancy, as did a large ovarian tumor and fibroid

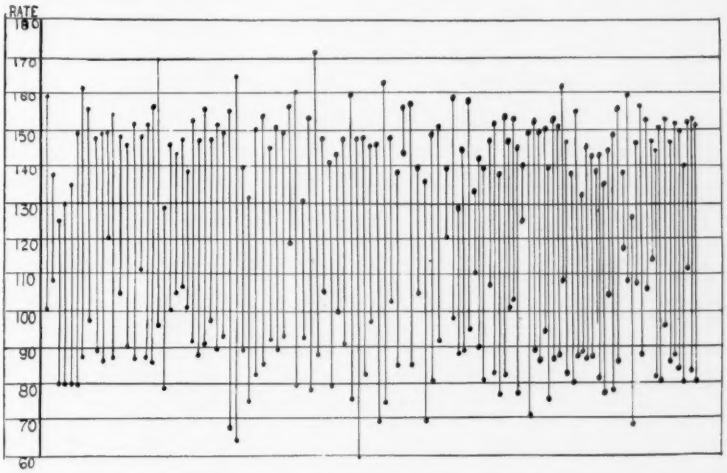

Fig. 6.—Synchronous maternal and fetal heart rates are represented by each line for every reading. The upper end indicates the fetal rate and the lower end, the maternal heart rate. Note complete absence of constant relationship.

uterus, and a missed abortion. These three patients had negative fetal electrocardiograms. In four instances, fetal movements were not felt by the mother, and the fetal heart was inaudible to several physicians; but the fetal electrocardiograms were positive. These four patients all had viable babies.

Two patients had negative fetal electrocardiograms in the fifth month, and aborted macerated gestational products a short while later. One patient, who delivered a viable fetus prematurely at 215 days, had a positive fetal electrocardiogram. Another patient with jaundice, who prematurely delivered a baby weighing 2 pounds, 7 ounces, had a positive fetal electrocardiogram. In another case, two electrocardiograms taken forty-two and six days before labor, showed a rate of 172 and 232 beats per minute, respectively. The patient had an unsuspected gastrochisis fetalis with hydramnios. One patient, whose baby was stillborn, at term, had positive fetal electrocardiograms 138 and 110 days before delivery. The time of death may, therefore, be fixed after the one hundred and tenth day before delivery.

One patient, who had had a previous cesarean section before delivery, became sick with vague abdominal symptoms in the seventh month. The electrocardiogram was negative. Ten days later, cesarean delivery of a dead fetus through a ruptured uterus was performed. One patient had twins. Electrocardiograms taken on the day of delivery showed two sets of fetal deflections. The record was a poor one since the mother was having labor pains.

Since the completion of this work and while this paper was being written, 14 of our patients have delivered spontaneously. All fourteen had positive fetal electrocardiograms. None of these, however, are included in this series.

Cardiac arrhythmias in the mothers were rather rare except for the usual sinus and respiratory arrhythmias of varying degree. In two instances, ventricular extrasystoles were recorded, and one patient exhibited transient sinus block, without any evidence of cardiac distress. The fetal heart rates generally showed a moderate degree of sinus arrhythmia, the rate on successive counts varying by as much as 30 beats per minute with an average fluctuation of about 10 beats per minute. In two instances, the record was strongly suggestive of fetal extrasystoles, although the exact nature of the extrasystole could not be determined. In one instance, the fetus exhibited a varying degree of partial block with a rate ranging from 144 per minute to as low as 63 per minute. After birth, this baby exhibited no cardiac abnormality. The anomaly, ectopia cordis, produced peculiar electrocardiograms.

CONCLUSIONS AND SUMMARY

In summarizing the results described in the preceding pages, the following conclusions may be stated:

1. A fair sample, consisting of the first 100 consecutive full-term pregnancies, terminated by normal labors, was studied. In this sample, an almost equal number of parous and nulliparous, white and negro women of all ages, is found. Vertex presentations singularly occurred in all but 4 cases. The number of male and female infants was almost similar.

2. Constancy of method, technique, and personal error was maintained since all tests were performed by one of the authors.

3. A cursory outline of historical data is briefly mentioned along with the technical difficulties previously experienced.

4. A new technique, describing variations in position of electrodes as well as the small convenient portable electrocardiographic instrument, is described. Several complications, inherent physical disturbances, which may alter or obstruct clear recordings, are pointed out. Generally, larger, more obese women yielded inferior electrocardiograms.

5. Only two patients of the entire group failed to exhibit satisfactory fetal curves at some time during pregnancy.

6. Ninety-eight out of 100 patients showed one or more satisfactory curves. The maximum number of records of any single patient was 4.

7. Seventy-five per cent of 153 tests performed on 100 patients showed clear-cut curves. Those which were not clear were considered negative.

8. No positive electrocardiograms were obtainable earlier than the fourth lunar month. In this month, 33 per cent of 9 readings were positive. In the third month no records were successful.

9. The individual monthly percentages of positive results ranged from 53.8 to 96.5 per cent. The average of all monthly percentages, from the fourth to tenth lunar months, inclusive, was 77.86 per cent.

10. In the last two months combined, it is significant that a total of 48 readings yielded 96 per cent positive readings.

11. The fetal heart rate is no index as to the fetal sex, since both sexes averaged 148.7 beats per minute. No correlation between the rate and color of the fetus is found.

12. There was a tendency for a gradual but definite decline in the fetal heart rate to the eighth lunar month; from then on to delivery there was a slight rise. The duration of the pregnancy in any instance cannot be estimated by the rate.

13. Fetal and maternal rates cannot be correlated; a change in one did not necessarily accompany a corresponding alteration in the other.

14. The electrocardiogram furnished a reliable diagnostic test in pseudocyesis of the menopause, suspected pregnancy due to amenorrhea with a large fibroid and huge ovarian cyst, as well as a missed abortion.

15. Electrocardiograms successfully indicated fetal viability in 4 instances in which fetal movements were not felt and in which the fetal heart was inaudible.

16. The presence of multiple pregnancies was accurately diagnosed in one case.

17. A marked rate increase in two cardiograms taken thirty-five days apart within six weeks of labor, proved to be due to an unsuspected anomaly, gastroschisis fetalis with hydramnios.[6]

18. In another teratologic birth, thoracoabdominoschisis with anencephalus, in which the apex of the fetal heart was drawn cephalad in a 180° version by congenital adhesions, the T-waves were inverted. This suggests the possibility of determining a breech presentation.

19. Generally, fetal hearts show sinus arrhythmias and occasionally show extrasystoles and varying degrees of partial block.

20. Intrauterine anomalies usually produce peculiar electrocardiograms in which the rate shows a marked rapidity.

21. Before cesarean section is performed in instances of doubtful viability, an electrocardiogram is indicated.

22. Electrocardiography with the above technique and new instrument was found by us to be a practicable procedure in all pregnancies between the fourth and tenth lunar months.

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GLOMERULAR FILTRATION AND RENAL BLOOD FLOW IN THE TOXEMIAS OF PREGNANCY

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SINCE Smith, Goldring and Chasis[1] described the use of "diodrast" at low plasma levels for measuring "effective renal blood flow" this test has been used in several laboratories and has been found to have definite bearing on several clinical entities in which the kidney was suspected but in which previously known renal function tests were found to be normal, namely "essential" hypertension and arteriolar disease.[2]

The use of inulin as a measurement of glomerular filtration in man[3] has also added markedly to the physiologic exploration of renal function and has proved of value in differentiating parenchymatous renal disease from arteriolar disease.[4]

Diodrast in the pregnant woman was first used by Chesley,[5] who was trying to demonstrate a relationship of "the toxemias" to the hypertensive diseases of the nonpregnant patient.[6] He was unable to find any evidence of decreased renal blood flow in patients with "toxemias of pregnancy." A similar work was done by Corcoran and Page,[7] who found significant alteration in blood flow in some of these patients and also found in some of them a noticeably decreased inulin clearance. Welsh, Wellen, and Taylor[8] have recently shown that in ante-partum patients the inulin clearance is decreased and the diodrast clearance normal or high, and that post partum both clearance values fall.

Because of the high incidence of hypertension following the "toxemia syndrome," we consider it unlikely that the diseases are entirely unrelated; therefore this previous work has been repeated in an effort to classify the clinical stages noted and to show thereby the relationship of "the toxemias" to the hypertensive diseases of the nonpregnant patient.

MATERIALS AND METHODS

Thirty patients were included in this series, and the abnormal patients were classified by the nomenclature recently adopted by the American Committee on Maternal Health.[9]

Eight patients who were within one month of term, had had no previous history of hypertension or toxemia of pregnancy, and who had had no elevation of blood pressure, changes in the retinal vessels or albuminuria during this pregnancy were used as normal controls.

Ten patients who had albuminuria of more than 2 Gm. per day, hypertension, in most cases also edema and a rapid weight gain, but who had no antecedent history of "toxemia of pregnancy" or of hypertension, and whose retinal vessels showed no more than spasm were classified as patients having "severe pre-eclampsia."

Ten patients who had hypertension of moderate to marked degree, some of whom had albuminuria of mild to moderate degree, and who had a previous history of hypertension, eye ground changes, and who usually had had previous "toxemic" pregnancies were classified as having "hypertensive disease."

All clearances were run by the same individual and a standard technique was used:

One thousand cubic centimeters of water were given by mouth the night preceding the test, and 200 c.c. were given at 5:00, 5:30, and 6:00 on the following morning. The bladder was catheterized at 6:00 A.M. with a No. 14 soft rubber catheter and an intravenous drip started at 4 c.c. per minute containing 500 c.c. of 5 per cent glucose, 15 c.c. of 10 per cent inulin* and 15 c.c. of diodrast.† In order to attain an immediate high blood level, a priming solution of 10 c.c. of 10 per cent inulin solution and 1 c.c. of diodrast was given as the drip was started. After a fifteen- to twenty-minute period had elapsed to allow the blood and urine to reach an equilibrium, the bladder was inflated with 50 to 100 c.c. of air three times to expel the remaining urine. From this last expulsion of air to the last expulsion at the end of the clearance, the time was accurately measured to the closest one-half minute. The clearance periods were varied in length in inverse proportion to the urine flow and an effort was made to secure around 80 to 120 c.c. of urine. The usual ante-partum clearance lasted on normal or hypertensive patients from ten to thirty minutes and on toxemic patients from twenty to sixty minutes. Post partum all clearances were run from ten to twenty minutes. Three clearances were run on each patient consecutively in this manner and no attempt was made to keep the urine flow maximum.

Several difficulties have been encountered in doing clearances on women at term. "Pockets" of urine may accumulate in the bladder, which can be found and expressed only with difficulty and which can be missed. It has also been noted in patients with pre-eclampsia and occasionally in the normal that adequate urine flows are impossible to attain. Therefore, we have run clearances at low urine flows on our normal controls and have found that accurate clearances are not obtained for some patients until 1 c.c. a minute and sometimes more has

*Inulin was obtained from the Pfanstiehl Company, Waukegan, Illinois.

†We wish to thank the Winthrop Chemical Company, New York, for part of the diodrast used in this study.

been reached. For this reason, no clearances were figured in the totals where urine flows were less than 1 c.c. per minute, unless they could be checked by comparable values at adequate flows.

Blood samples were taken in the middle of the first and third clearances and values interpolated for the blood values of the second clearance.

Plasma was used in all determinations except urea which was done on whole blood. The plasma and urine were precipitated by the Somogyi technique after incubating each with yeast* for one and one-half hours or more at 37° C. Inulin was determined by the method of Alving, Rubin, and Miller.[10] Diodrast in the earlier experiments was determined by Rolf and White's[11] method by hand cooking each tube (we found that the water bath method in our hands did not give constant results). The extraction factor for the blood by this method was considered 86 per cent. The later diodrast determinations were done by Alpert's[12] method. Urea was determined by the manometric method of Van Slyke.[13]

The filtration fraction was determined by $\frac{\text{Inulin clearance}}{\text{Diodrast clearance}}$, the renal blood flow by $\frac{\text{Diodrast clearance}}{1 - \text{Hematocrit}}$. Total serum proteins were done on most patients.

All clearances were rejected which failed to check within 10 per cent of the mean for all three clearances run at the same time. However, in cases in which one of the tests was known to be technically incorrect, this one test was discarded. Where doubt existed as to the validity of the results, clearances were generally checked on another day.

All clearances were calculated on the basis of 1.73 square meters of ideal surface area.

RESULTS

Normal.—The inulin clearance on the normal pregnant patient averaged 116.1 ± 16.9 c.c. per minute (90 to 158 c.c. per minute). There are no inulin clearances available in the literature at this time, but this figure corresponds well with those for normal women reported by Goldring, Chasis, Ranges, and Smith[14] as 118.7 ± 17.5 c.c. per minute. Post partum we found that the normal inulin clearance rose to 139.3 ± 16.1 c.c. per minute (98 to 170 c.c. per minute). (Table I.)

The diodrast clearance in the normal ante-partum patient was found to be 636.5 ± 145.4 c.c. per minute (445 to 860 c.c. per minute), which corresponds to Chesley's[5] 610 c.c. per minute and that found in normal nonpregnant persons by Goldring[14] of 600.4 ± 87 c.c. per minute. Post partum this clearance was found to be altered insignificantly and the mean was 630.1 ± 90.7 c.c. per minute (438 to 870 c.c. per minute).

The renal blood flow was found to be 950.0 ± 236.7 c.c. per minute (670 to 1,380 c.c. per minute). This seems slightly higher than that

*We wish to thank the Fleischmann Company of New York for supplies of starch-free yeast used in this study.

TABLE I. SUMMARY OF THE DATA ON PATIENTS WHO ARE APPARENTLY CLINICALLY NORMAL†

PATIENT	AGE	PARITY	WEEK	BLOOD PRESSURE MM.Hg	ALBUMIN	HEMATOCRIT %	INULIN CLEARANCE C.C./MIN.			DIODRAST CLEARANCE C.C./MIN.			RENAL BLOOD FLOW C.C./MIN.			URINE FLOW C.C./MIN.			FILTRATION FRACTION			UREA CLEARANCE C.C./MIN.		
A-1	31	5-3-2	41	115/78	Neg.	36	90			512			890			0.9			0.15			360.0*	43.3*	
				120/80	Neg.	40	136	125		870	700		1,425	1,160		2.4	1.4		0.16	0.18		648.0	56.1*	
A-2	21	0-0-0	37	110/70	Neg.	37	96	104		640			990			3.5	6.3	9.1	0.16			–		
				120/80	Neg.	41	111	120		660	580		1,120	980		1.0	3.0		0.17	0.20		62.6*	87.2	
A-3	31	2-1-1	40	120/85	Neg.	44	110	123	131	640	510		1,130	910		9.4	9.3		0.17	0.24		102.0	100.0	
				130/85	Neg.	44	98	113	103	610	640		1,100	1,113		6.6	4.1	7.6	0.16	0.18		64.2	76.5	
A-4	34	2-1-1	40	130/85	Neg.	34	123	117		445	640		700	970		2.5	3.2	6.1	0.27	0.18		137.4	158.1	
				100/70	Neg.	41	170	148		640	438		1,000	680		2.8	3.8	7.6	0.26	0.32		131.4	108.5	
A-5	40	3-1-2	38	120/80	Neg.	37	56*	59*		500	373		790	470		1.7	1.3		0.11	0.16		70.1*	58.3*	
				110/70	Neg.	32	154	154	136	550	490		810	720		7.7	4.6	2.4	0.28	0.31		115.8	133.0	
A-6	24	2-1-1	38	120/70	Neg.	32	128	90		820	478		1,200	670		2.3	0.9		0.16	0.19		76.6	56.4*	
				110/80	Neg.	35	158	156		750	650		1,150	1,000		6.7	6.4		0.21	0.24		105.4	89.0	
A-7	25	1-0-1	32	120/70	Neg.	39	92	126	101	484	560	540	790	925	890	2.7	5.6	4.2	0.19	0.27	0.18	116.4	74.7	
				110/60	Neg.	45	150	150		510	410		930	740		3.5	6.3		0.29	0.36		136.1	125.8	
A-8	32	2-1-1	40	120/80	Neg.	34	142	143		910	860	790	1,380	1,300	1,196	6.4	4.0	3.0	0.15	0.16		86.6	88.0	87.2
				110/70	Neg.	35	120	148	147	582	620	600	880	940	910	1.7	4.5	1.0	0.20	0.23	0.24	72.4	81.1	74.9
Mean Ante partum							116.14			636.5			950.0						0.176			96.23		
σ							±16.9			±145.4			±236.7									±23.2		
2σ							±33.8			±290.8			±473.4									±46.4		
Mean Post partum							139.37			630.1			979.8						0.234			100.5		
σ							±16.1			± 90.7			±185.8									±25.7		
2σ							±32.2			±181.4			±371.6									±51.4		

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

†In all tables the first line for each patient represents findings ante partum and the second line findings post partum.

reported by Chesley, but only because approximately half of his patients had a moderate to severe anemia (hematocrit 26 to 31.7 per cent). Post-partum renal blood flow averaged 979.8 ± 185.8 c.c. per minute (680 to 1,425 c.c. per minute).

The filtration fraction was found to average 0.176 (0.15 to 0.29) ante partum and 0.234 (0.16 to 0.36) post partum in these normal patients.

The urea clearances averaged 96.2 ± 23.2 c.c. per minute (76.6 to 158.1 c.c. per minute) ante partum, and 100.5 ± 25.7 c.c. per minute post partum.

Pre-eclampsia.—In patients with the clinical diagnosis of pre-eclampsia, the inulin clearance ante partum was found to be 84.0 ± 35.3 c.c. per minute, which represents a significant decrease. The range, however, is noted to be quite wide (24 to 160 c.c. per minute) and one-third of these cases had a normal clearance. One was definitely elevated above normal. It is noted that patients with a moderate elevation of blood pressure and severe albuminuria usually have a low urine flow and a low inulin clearance, although not without exception (Table II).

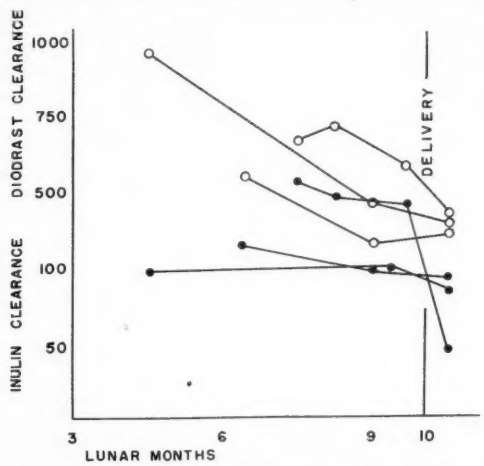

Fig. 1.—Diodrast and inulin clearances in 3 cases of hypertensive disease throughout the period of gestation.

The diodrast clearance in these patients is found to average 680.1 ± 283 c.c. per minute, and to be characteristically normal. A wider variation is noted here than in the normal (178 to 1,440 c.c. per minute) but 50 per cent are easily within normal range.

The filtration fraction is moderately reduced and a few very low values are noted. The urea clearance is definitely depressed (75.1 ± 18 c.c. per minute); the range is probably of no value since a large number of our determinations had to be discarded because the augmentation limit of the urea clearance was below the urine flow.

Post partum we noted a rise in inulin clearance (105.1 ± 38.5 c.c. per minute) such as that in the normal patient, but still not to normal levels. The distribution is wider than normal (35 to 164 c.c. per minute) although the range is normal in more than half of the cases and in them there is a definite tendency toward "high normal" values.

The diodrast clearance post partum shows a definite fall (481.9 ± 179.0 c.c. per minute); here the range is wide (268 to 810 c.c. per

TABLE II. SUMMARY OF THE DATA ON PATIENTS WITH THE CLINICAL DIAGNOSIS OF PRE-ECLAMPSIA

PATIENT	AGE	PARITY	WEEK	BLOOD PRESSURE MM. Hg	ALBUMIN	HEMATOCRIT %	INULIN CLEARANCE C.C./MIN.			DIODRAST CLEARANCE C.C./MIN.			RENAL BLOOD FLOW C.C./MIN.			URINE FLOW C.C./MIN.			FILTRATION FRACTION			UREA CLEARANCE C.C./MIN.		
B-1	22	1-0-1	38	135/ 90	+++	35	110	78		460	317		700	490		1.6	1.1		0.24	0.25		56.3*	36.4*	
				140/ 90	+	43	132	150		520	580	610	910	1,020	1,030	2.4	2.5	3.5	0.25	0.24		118.6	113.6	
B-2	32	1-1-0	40	150/120	++	38	80	107		327	450		530	725		3.9	4.1		0.24	0.24		61.3	54.7	57.6
				140/ 90	Neg.	38	145	145		460	310	268	740	500	432	6.1	6.5	2.8	0.31	0.46		84.9	68.5	
B-3	24	1-0-1	39	160/105	++++	36	61	52		492	520	452	770	812	704	4.9	5.0	3.9	0.12	0.11		85.3	72.2	
				140/ 90	Tr.	42	138	140	141	520			900			5.8	5.8	12.6	0.26			61.9	51.0	
B-4	25	1-1-0	34	160/105	Tr.	37	90	89		610			970			1.4	1.4		0.15			49.2*	42.5*	
				130/ 90	++	40	138	140	141	770	645	690	920	1,020	930	6.7	5.7	5.9	0.25	0.23	0.20	66.4	72.7	74.2
B-5	34	0-0-0	40	160/100	Tr.	36	160	149		610	570		1,000	900		2.5	2.5		0.26	0.26		86.1	114.9	
				140/100	Neg.	35	35	35	39	348	373	353	495	535	505	4.7	3.8	5.1	0.10	0.09	0.11	57.8	63.5	62.7
B-6	27	0-0-0	38	150/100	++++	39	140	91		690	494		1,120	810		1.3	0.8		0.20	0.18				
				140/ 90	+	38	98	90		323	370	356	520	600	530	5.6	5.5	5.2	0.30	0.24		68.1	66.1	65.0
B-7	22	0-0-0	36	140/ 90	++++	34	90	123	109	942	1,440	1,185	1,460	2,200	1,850	0.95	2.6	3.2	0.09	0.08	0.09	84.6	63.8	
				135/ 85	+	37	110	118		790	800	810	1,250	1,260	1,280	5.9	5.2	6.9	0.14	0.14		122.1	134.1	134.2
B-8	30	1-1-0	39	140/ 90	++++	41	37	43	48	342	315	345	580	540	580	1.0	0.7	0.6	0.11	0.14	0.14	45.7*	28.9*	26.5*
				130/ 80	Tr.	33	164	134		372	374	432	600	620	700	5.7	6.2	7.0	0.27	0.19		110.8	110.4	120.6
B-9	22	0-0-0	38	150/100	++++	36	45			292			455			1.2			0.15			33.6*		
				135/ 85	+	38	113	129		372	374	432	600	620	700	5.9	6.4	8.0	0.30	0.34		93.2	110.1	115.9
B-10	40	3-0-3	40	140/100	+++	34	24	28		187	178		285	270		0.6	0.6		0.13	0.16		41.3*	46.0*	
				140/100	+	40	74	64	64	322	330	346	536	550	576	0.4	0.7	0.6	0.23	0.19	0.18	57.0*	53.8*	
Mean Ante partum							84.0			680.1			905.0						0.167			75.11		
σ							±35.3			±283.2			±425.5									±18.0		
2σ							±70.6			±566.4			±851.0									±36.0		
Mean Post partum							105.1			481.9			745.7						0.228			89.0		
σ							±38.5			±179.0			±192.6									±25.7		
2σ							±77.0			±358.0			±385.2									±51.4		

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

TABLE III. SUMMARY OF THE DATA ON PATIENTS WITH THE CLINICAL DIAGNOSIS OF HYPERTENSIVE DISEASE

PATIENT	AGE	PARITY	WEEK	BLOOD PRESSURE MM. HG	ALBUMIN	HEMATOCRIT %	INULIN CLEARANCE C.C./MIN.			DIODRAST CLEARANCE C.C./MIN.			RENAL BLOOD FLOW C.C./MIN.			URINE FLOW C.C./MIN.			FILTRATION FRACTION			UREA CLEARANCE C.C./MIN.		
C-1	33	2-0-1	37	140/ 90	Tr.	40	76	70		330	280		550	468		1.3	0.9		0.23	0.25		57.4*	48.9*	
				135/ 90	Neg.	40	119	100		290	330		485	550		5.3	1.2		0.41	0.30		36.2	24.3*	
C-2	23	1-1-0	41	160/110	++	44	12	15		195	180		350	320		0.2	0.2		0.06	0.08		28.2*		
				140/ 95	Tr.	43	38	25		210			368			0.4	0.16		0.18			58.6*	83.0*	
C-3	35	7-1-5	40	135/ 90	+	40	82			130	135		220	230		1.4	0.6		0.63					
C-4	34	3-1-1	39	150/ 90	Tr.	37	35	30		200			318			4.9	1.7		0.17			67.9		
				140/ 90	Neg.	34		76	84	472	450	460	715	680		6.1	6.4		0.16	0.19		61.0	55.3	
C-5	28	0-0-0	28	170/130	Neg.	40	144			500	590	600	830	980	1,000	1.8	2.5	3.5	0.29			101.0	119.0	
				150/100	Neg.	38	128	123	119	580	530	495	935	854	798	9.3	6.9	6.7	0.22	0.23	0.24	119.8	114.3	98.6
C-6	30	5-1-4	38	150/100	Neg.	38	86	99		408	383		658	618		0.8	0.5		0.21	0.26		31.6*	27.3*	26.0*
				160/110	+	40	90	88		350	335		580	550		6.8	6.3	3.0	0.25	0.26		62.4	64.0	
C-7	23	1-0-1	39	160/110	Tr.	34	112	115		393	286		590	435		7.4	3.2		0.28	0.40		52.5*	35.2*	57.6*
				130/ 90	Neg.	32	101	131		344	333		510	490		4.6	2.5		0.29	0.39		91.6	112.9	
C-8	43	7-5-0	40	200/120	Neg.	38	102	86		312	362		500	590		1.8	1.2		0.32	0.23		80.6*	54.0*	
				150/110	Neg.	40	86	74	73	430	428	380	716	714	670	4.4	6.2	7.4	0.20	0.17	0.19	77.1	83.4	83.3
C-9	38	0-0-0	40	180/110	+++	44	47	53	80	504	500	570	900	890	1,004	9.3	6.4	3.7	0.09	0.10	0.14	57.6	57.3	64.5
				150/100	+	33	80	78	100	410	412		610	620		1.9	1.2	4.7	0.19	0.19		45.7*	41.5*	66.6
C-10	34	2-1-1	38	160/100	Neg.	37	154	143		1,090	900		1,700	1,420		3.0	6.4		0.14	0.16		111.1	146.3	124.6
				150/ 90	Neg.	40	144	123	142	610	606	625	1,020	1,020	1,030	5.9	7.0	9.3	0.24	0.20	0.23	103.5	106.9	122.2
Mean Ante partum							87.06			514.8			693.8						0.228			95.4		
σ							±34.2			±234.3			±414.5									±31.0		
2σ							±68.4			±468.6			±828.6									±62.0		
Mean Post partum							95.28			464.52			710.2						0.234			88.4		
σ							±31.9			±114.8			±193.7									±24.6		
2σ							±63.8			±229.6			±387.4									±49.2		

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

minute) but half the values are definitely low. A concomitant fall in the renal flow was noted (745.7 ± 192.6 c.c. per minute).

The filtration fraction is normal in average and range.

Urea clearance values tend toward normal but are still below normal post-partum values.

Hypertensive Disease.—The inulin clearance in this group also shows a noticeable reduction (87.0 ± 34.2 c.c. per minute) and the range is quite wide (12 to 154 c.c. per minute); almost one-half of the cases are definitely low. The lowest clearances were obtained in those patients having albuminuria and low urine flows. It is noticeable that two of these patients had a relatively severe type of arteriolar disease (one had hemorrhages in the eye grounds, severe albuminuria and a long history of hypertension and the other 28 years old had a pressure early in pregnancy of 200/130 mm. Hg), yet each had an entirely different clinical course and clearance value.

The diodrast clearances show a definite depression in the ante-partum period (514.8 ± 234.3 c.c. per minute) and the range of values is quite great (130 to 1,090 c.c. per minute) but more than half are definitely low and only one shows a high value (Table III).

The renal blood flow is depressed both ante partum and post partum (693.8 ± 414 and 710.2 ± 193 c.c. per minute).

The filtration fraction is elevated to 0.228 and the range is quite great (0.06-0.41) and most of these values are definitely elevated. When this value is very low there is always also a large decrease in renal blood flow.

The urea clearance is definitely depressed both ante partum and post partum, approximately equivalent to the value noted in patients with pre-eclampsia in the post-partum period (88.4 and 89.0 c.c. per minute) but is not so low as the value found in this group ante partum (95.0 as compared to 75.1 c.c. per minute).

DISCUSSION

It seems obvious from this and previous studies[7, 8] that the ante-partum inulin clearance is reduced in patients with pre-eclampsia and also in those with hypertensive disease. Renal blood flow in the pre-eclamptic patients is characteristically normal in the ante-partum period, while in the hypertensive group this value is definitely reduced.

Post partum the inulin clearances in both groups tend to return to normal, but the renal blood flow is reduced in both the pre-eclamptic and hypertensive groups, *almost equally* in amount.

The filtration fraction, which has been stressed by Corcoran,[7] is found to be moderately reduced in our patients with pre-eclampsia and high in the hypertensive group.

The urea clearance is found to be reduced in both groups, more noticeably in the pre-eclamptic series. This is compatible with findings repeatedly reported.[15, 16]

The value of these studies in the clinical differentiation of patients would seem obvious in some cases. If the patient in the ante-partum period had a low renal blood flow with either a high or low glomerular

filtration, it would be probable that she had a hypertensive disease, and if the renal blood flow were normal, the filtration low, pre-eclampsia would be the likely classification. If both values are normal or high, however, no answer is given to the problem.

Real value could be attached to the test post partum, in addition to careful clinical follow-up, particularly after several months or years. It might then be possible to determine the presence of subclinical or nonhypertensive vascular disease by means of these tests and to be guided by them in allowing the patient to accept responsibility of another pregnancy, assuming that pregnancy causes further damage to patients with vascular disease.

The real interest and value in these tests, however, seems to lie in the study of the physiologic function of the various portions of the kidney associated with this complication of pregnancy.

It is likely that no difference in fundamental pathology exists among those patients who have "toxemia of pregnancy" whether the renal blood flow and filtration rates are high or low, but that functional changes in vascular dynamics are causing these alterations in the mechanism of excretion. This is substantiated by the finding of a wider range of values among "toxemic" patients for diodrast and inulin clearance than that noted among normal patients.

Since the renal blood flow of "toxemic" patients immediately falls post partum to levels below normal and since a clinical diagnosis of one of the syndromes accompanied by hypertension (nephritis, hypertensive disease, etc.) can be made in 40 to 50 per cent of these cases if followed clinically for ten years or more, it would seem that "preeclampsia" and "hypertensive disease" are stages in the same process, differing only in that the degree of severity of the disease for these patients as for the nonpregnant hypertensive[17] determines the change in renal blood flow and in filtration fraction.

If we assume that these patients all have the same fundamental disease process, we should be able to show its similarity to that which obtains in the nonpregnant hypertensive as we have been able to find no increased incidence of hypertension in women who have had pregnancies and those who have not been exposed to this hazard.[18]

The consistent findings in "hypertensive diseases" in the human being have been: reduced renal blood flow,[2, 17] an absolute reduction in glomerular filtration,[17, 19] and an increased filtration fraction.[2, 17] The basis for these findings has been interpreted as efferent arteriolar constriction, but it seems probable that both afferent and efferent arterioles have increased tone and that the efferent arteriolar constriction is predominant. In these "toxemic" women, we find reduced renal blood flow but also a reduction in filtration fraction. This has been explained by Corcoran[7] as due to a decreased permeability of the glomerular mem-

brane, but it would seem likely that the glomerulus, as in the nephrotic individual,[20] has an increased permeability and should be able to filter faster because of the increased pore-size, so that the picture could better be explained by increased afferent arteriolar tone.

We produced a syndrome in pregnant animals (rabbits and dogs) characterized by albuminuria, hypertension, convulsions, and death with necrosis in the liver, kidney, myocardium, and placentas, by constricting the renal arteries during pregnancy.[21] We found, however, that the typical syndrome was produced only by minimal constriction of these arteries, and that uremia followed severe constriction.[22] Since that time, Schroeder[23] has shown that the renal blood flow in animals with minimal to moderate constriction of these arteries was normal, while it was only after severe constriction that the renal flow was reduced. This work has been confirmed by Page,[24] who has shown that the hypertension is dependent on reduction of pulse pressure behind the renal artery clamp.

We have followed three patients with "hypertensive disease" from the earlier parts of gestation through delivery and have observed that pregnancy itself apparently furnishes a factor which tends to keep renal blood flow elevated until the latter part of pregnancy when it drops to lower levels and becomes definitely depressed following delivery.

It would seem likely that the same mechanism for the production of hypertension applies to the woman with "toxemia of pregnancy" as to the nonpregnant hypertensive. The disease is modified by the pregnancy in a quantitative way in that the renal blood flow is maintained despite renal arteriolar constriction of moderate degree and qualitatively in that the afferent arteriolar tone is increased to a greater extent than in the nonpregnant hypertensive, but both differences are merely quantitative modifications of the same fundamental vascular abnormality.

SUMMARY AND CONCLUSIONS

Inulin and diodrast clearances have been done on 10 patients with "pre-eclampsia" and 10 patients with "hypertensive disease."

"Pre-eclampsia" is characterized by a decreased rate of glomerular filtration, a normal renal blood flow and a decrease in the filtration fraction.

Patients with "hypertensive disease" have reduced glomerular filtration and renal blood flow but an elevated filtration fraction.

In both groups of patients post partum the glomerular filtration tends to return toward normal and in both groups the renal blood flow falls well below the normal level.

Evidence is presented in support of the theory that the same fundamental vascular abnormality is responsible for the hypertensive diseases as for the "toxemias of pregnancy" and their sequelae.

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APLASTIC ANEMIA IN PREGNANCY

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INTRODUCTION

THE first case of aplastic anemia, noted in the literature, was described by Ehrlich[1] in 1888, and occurred in a young pregnant woman. Although authenticated instances of aplastic anemia in pregnancy since that time are very few, they present an important problem in obstetric management.

Whether idiopathic aplastic anemia is a true "anemia of pregnancy" or is a coincidental, unrelated phenomenon is still open to question. It is well recognized that any of the blood dyscrasias, as for example acute hemolytic anemia,[8] sickle cell anemia,[9] idiopathic purpura hemorrhagica,[10] and leucemia[11-13] may become clinically manifest during the pregnant state. However, in view of the fact that idiopathic aplastic anemia is known to have abated following abortion and in view of other considerations discussed below, it appears that this disease may be a severe, specific complication of the pregnant state.

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There is a dearth of material on this subject in the standard reference works of obstetrics and hematology,[14-17] and in recent reviews of anemia in pregnancy.[2-7] In 1931, Baize[18] collected from the literature 96 cases of idiopathic aplastic anemia, of which 47 occurred in women. Additional reported instances in women since that time bring the total up to 80. The thirteen cases of obstetric interest that are included in this group will be analyzed below.

In many of the case reports of aplastic anemia, the clinical diagnosis lacks biopsy or autopsy confirmation. A case in point is that of Parkes Weber,[19] previously reported as aplastic anemia, found at post mortem to be leucopenic myelosis. Other cases, on close inspection, prove to be instances of pernicious anemia, hematopoietic depression secondary to sepsis, carcinomatosis of the bone marrow, etc. On the other hand, known etiologic agents such as arsenic, benzol intoxication, or irradiation with roentgen rays must be rigidly excluded before a given case may be considered as truly "idiopathic."

Our interest in this subject was stimulated by the occurrence of a case of aplastic anemia in a young pregnant woman, with a rapidly fatal issue.

REPORT OF CASE

Clinical History.—The patient was a 27-year-old white woman, a native of New York, and a typist by occupation. She entered The Mount Sinai Hospital on April 19, 1939, on the medical service of Dr. George Baehr, complaining of profuse bleeding from the gums. The family history was irrelevant. The past history revealed diphtheria during childhood, and a tonsillectomy in 1934. In 1937, the patient's first pregnancy was terminated by curettage.

The last menstrual period occurred three months prior to admission. Shortly thereafter the patient experienced intermittent vomiting, which at times contained brown material. Two months before admission she noted the sudden onset of headaches and subconjunctival hemorrhages. Mild gingival bleeding, previously present, became accentuated, with progressive, spontaneous oozing during the six weeks before admission. In the last three weeks the gingival surfaces had been covered with blood clots.

A fortnight before coming to The Mount Sinai Hospital the patient vomited brownish material and fainted. A blood count at that time revealed a hemoglobin value of 28 per cent (Sahli); erythrocytes 1,800,000 per c.mm.; leucocytes 3,000 per c.mm. of which 90 per cent were lymphocytes; and platelets 30,000 per c.mm. Physical examination was essentially negative except for a few purpuric areas in the skin and profuse intermittent bleeding from the gums. The patient was admitted to another hospital, where she was given five transfusions, parenteral liver extract, and snake venom with no apparent effect. Only a very small amount of material was obtained by a sternal marrow puncture, practically all of the cells being members of the lymphatic series. In a searching history no story of drug ingestion, either as abortifacient or as sedative, or of exposure to noxious substances could be elicited. The patient and her family were emphatic in stating their desire to have the baby.

Physical Examination.—On admission to the Hospital, examination disclosed a well-developed, well-nourished young woman, markedly pallid

and prostrated. The temperature was 101.4° F., pulse 120, and respirations 24. There was a constant ooze of blood from the mouth. No lymphadenopathy was found other than tender submaxillary nodes. A harsh systolic murmur was heard over the entire precordium. The heart and lungs were otherwise not remarkable. The blood pressure was 120 mm. systolic and 60 mm. diastolic. The spleen was not palpable. The uterus was enlarged and soft, rising halfway to the umbilicus; the cervix was very soft. The skin was dry and somewhat scaling, and in places was almost parchment-like.

Laboratory Data.—The following values were obtained on examination of the blood: hemoglobin 42 per cent; erythrocytes 2,230,000 per c.mm.; leucocytes 1,050 per c.mm., of which polymorphonuclear cells were 5 per cent, lymphocytes 94 per cent, and monocytes 1 per cent, and platelets 20,000 per c.mm. Further blood counts are detailed in Table I. The erythrocyte sedimentation time was ten minutes. Both the blood sugar and the urea nitrogen were within normal limits, but the total proteins were low, 4.5 Gm. per 100 c.c. The blood Wassermann reaction was negative; the blood group was 2A. A trace of albumin and occasional leucocytes were found in the urine. The Aschheim-Zondek test for pregnancy was positive. No essential deviations from the normal were seen in the electrocardiogram.

Course and Treatment.—The patient remained alive in the hospital for a period of two and one-half weeks, during which time there was practically a continuous flow of blood from the gums. This could not be controlled by local hemostatic agents, compound bite-blocks applied to the oozing areas as compression splints, and continuous suction under the care of special nurses. During the last week there was also profuse nasal bleeding which required posterior nasal plugs for control. The temperature showed daily elevations between 101° and 102° F. The patient received 16 transfusions of citrated blood. The question of a possible relationship between the pregnant state and the aplastic anemia was raised and the advisability of performing a therapeutic abortion was considered. However, the general condition of the patient never improved sufficiently to make such a procedure feasible.

During the last three days of life, the patient developed progressive edema of the face and vulva. The temperature gradually rose from normal to 106.6° F. On the day before demise, she spontaneously aborted a well-formed male fetus about fourteen weeks of age. Following the abortion there was little vaginal bleeding and apparent cessation of gingival and nasal hemorrhage. The placenta failed to separate and could not be delivered despite instrumentation and the intensive use of oxytocics. Notwithstanding a continuous transfusion, the patient developed generalized purpura and died within twenty-four hours of the abortion, in a delirium of a kind suggestive of hemorrhagic encephalitis.

Pertinent Findings at Necropsy.—The autopsy (No. 11,158), was performed five hours after death. Widespread purpura was present, with extensive petechiae and ecchymoses of the skin, serosal surfaces of the pericardium, pleura, and peritoneum, diaphragm, heart, mucosa of the mouth, stomach, intestines, renal pelves, right ureter, urinary bladder, and uterine cervix. The spleen weighed 200 Gm. and was soft and flabby. The cut surface disclosed a purple red glistening pulp with distinct gray pink follicles and normal trabeculae.

The bone marrow of the ribs, sternum, and vertebrae was yellow-brown in color and dry, except for the lumbar vertebral marrow which

had a faint pink hue. The ribs were extremely thin, and the marrow space appeared as a narrow yellow line.

The right ovary had a freckled blue and red appearance, was semi-firm in consistency, and measured 4 cm. in diameter. On section it was seen to contain a corpus luteum which measured 1.5 cm. in diameter. The left ovary was not remarkable.

The uterine fundus reached a height two-thirds of the way to the umbilicus. The uterus was quite firm and measured about 13 cm. in length, 7 cm. in width, and 5 cm. in depth. The vaginal portion of the cervix was very edematous, thick, ecchymotic, and soft. The vaginal mucosa was studded with purpuric spots. Almost the entire endometrial cavity was occupied by a placenta which was everywhere adherent without any evidence of separation, or even of a well-defined cleavage plane.

Microscopic Examination.—There was no evidence of extramedullary hematopoiesis. A moderate amount of iron was present in the liver, spleen, and bone marrow. A striking hypoplasia of the bone marrow was present. The vertebral marrow appeared slightly less hypoplastic than

TABLE I*

DATE	CITRATE TRANSF. C.C.	HG % SAHLI	R.B.C., MILLIONS/C.MM.	W.B.C.	STAB.	SEG.	EOS.	MONOS.	LYMPHS.	PLATELETS	RETICS.
4/ 5	1,000	28	1.80	3,000					90	30,000	
4/ 8		46	2.10	1,350	8	8			84	20,000	0.5%
4/ 9	500	42									
4/10	500	45	2.01								
4/11	500	50									
4/15		40	2.18	1,600	6		2	2	90	20,000	0.5%
4/18		37									
4/19	500	30	Admitted to The Mount Sinai Hospital								
4/20	500	42	2.23	1,050	3	2		1	94	20,000	
4/21	500										
4/22	500										
4/24	500	49	2.73	680	6			4	90	20,000	
4/25	500	52	2.38	750	2	4	1	2	91	40,000	0.5%
4/26		47									
4/27	500	40									
4/28	500	35									
4/29		33									
4/30	500	33									
5/ 1		34		950							
5/ 2	500	32		700	2				98		
5/ 3	500	32		800	6				94	30,000	
5/ 4	1,000	31		350							
5/ 5	1,000	32		300	8	2			90		
5/ 6	500			Died							

*The authors are indebted to Dr. Frank Bassen for the privilege of publishing his hematologic findings prior to the admission of the patient to this hospital.

that of the sternum and ribs. All the hematopoietic elements of the marrow were quantitatively reduced, being replaced by fat. The small foci of blood formation that were present were primarily those of erythropoiesis. There was a marked paucity of megalokaryocytes. Adult forms of the granulocytic series were very few.*

*The comparative hematology of the venous blood and sternal marrow in groups of nonpregnant and pregnant women has recently been described by Pitts and Packham.[20] The histologic bone marrow findings in a large series of refractory and aplastic anemias are given by Rhoads and Miller.[21]

The uterine muscle showed marked hemorrhagic extravasation. There was no evidence of a true placenta accreta.

Examination of the Fetus.—The fetus showed no gross abnormalities. There was no evidence of purpura. The measurements were: crown-rump, 11.5 cm.; crown-heel, 16 cm. These values coincide with the expected findings in a four-month-old fetus.

Histologically the bone marrow of the mid-humerus, mid-femur, and lumbar vertebrae was active, and without evidence of aplasia. As far as could be determined by comparison with a presumably normal fetus of about the same age, there were no significant changes in the bone marrow, spleen, liver, kidney, or other organs.

CASES OF APLASTIC ANEMIA DURING PREGNANCY

The initial case of aplastic anemia, described by Ehrlich[1] in 1888, was that of a 21-year-old female complaining of uterine bleeding. Curettage revealed fragments of fetal membranes. The erythrocyte count was 213,360 per c.mm. and there was a leucopenia with 80 per cent of the leucocytes being lymphocytes. The patient died within a month without any other bleeding manifestations. At autopsy the bone marrow was found to be yellowish throughout. As Ehrlich states, it was not possible to determine whether the profuse uterine bleeding was caused by an abortion or was the result of a hemorrhagic diathesis.

Because of confusion in terminology, it is difficult to evaluate many of the cases found in the literature, such as those described by Planchard[22] in 1887 and by Hanot and Legry[23] in 1889. That profound anemia of an aplastic type can occur with overwhelming infection has long been recognized. Such an instance is the case of Ricca-Barberis,[24] in 1908, of aplastic anemia in puerperal sepsis with fatal termination. Similarly, in 1906, Hirschfeld[25] reported a case developing after an abortion in a 34-year-old woman, with death in a few weeks. At postmortem there was found a gangrenous endometritis in addition to an aplastic bone marrow. There were no blood counts, but the patient had known melena for two months. In a second case described by Hirschfeld anemia was discovered in a 28-year-old parturient, with rapid progression and death in nine months. Necropsy disclosed a profound aplasia of the bone marrow.

The first case clinically approximating our own was reported by Massary and Weil[26] in 1908. A 21-year-old woman was seen in the fourth month of pregnancy, complaining of epistaxis of three months' duration, purpura of the legs for two months, and gingival bleeding for a few weeks. Physical examination revealed marked pallor, edema of the entire face, and a uterus enlarged to the size of a four months' pregnancy. The erythrocyte count was 776,000 cells per c.mm., and the leucocyte count 5,900 cells per c.mm., of which 58 per cent were polymorphonuclear leucocytes, 35 per cent lymphocytes, and 7 per cent monocytes. Death occurred from heart failure. The fetus and placenta were found to be grossly normal at autopsy. The bone marrow was yellow and poor in formed elements; however, the predominance of megaloblasts over normoblasts, with a decrease in polymorphonuclear cells in relation to myelocytes suggests that this actually may have been a severe case of pernicious anemia.

Jungmann,[27] in 1914, described the case of a 29-year-old woman who, at the termination of her third pregnancy, had a severe anemia until three weeks post partum. At the end of her fifth pregnancy she was found to be pale and weak, but not bleeding. The blood hemoglobin was 22 per cent, erythrocytes 1,220,000 per c.mm., and leucocytes 10,000 per c.mm. with 73 per cent segmented neutrophiles and 22 per cent lymphocytes. The blood smear showed myelocytes, nucleated red blood cells, macrophages, and a decrease in platelets. At delivery there was no excessive bleeding, and thereafter the patient made a complete recovery. Again, in view of the leucocyte count and the evidence of young forms in the smear of the peripheral blood, the validity of this as an instance of aplastic anemia is open to question. A more suggestive case is that of Larrabee,[28] concerning a 30-year-old woman in the third month of her second gestation, who complained of weakness, dyspnea, and vomiting. With the exception of two small superficial ecchymoses, there were no bleeding manifestations. The blood findings were: hemoglobin 20 per cent; erythrocytes 780,000 per c.mm., with 0.4 per cent reticulocytes and no normoblasts; platelets 64,000 per c.mm.; and leucocytes 2,600 per c.mm., of which 48 per cent were polymorphonuclears, 49 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. Despite two transfusions the patient died in three weeks, no attempt to terminate pregnancy having been made. No post-mortem examination was performed.

In 1938, Müller[29] reported the case of a 28-year-old woman whose second pregnancy terminated in a normal delivery. There was no excessive bleeding, and no vaginal examination had been performed. Following delivery she experienced fever and chills. The uterus was not abnormal, the blood culture was sterile, and there was no clinical or bacteriologic evidence of an infectious process. The blood values were: hemoglobin 25 per cent, erythrocytes 1,400,000 per c.mm., and leucocytes 5,200 per c.mm. with 1.5 per cent polymorphonuclear cells. Subsequently the patient developed petechiae and hemorrhages, her leucocyte count fell to 2,600 per c.mm., of which 84 per cent were lymphocytes, and her platelet count was 110,000 per c.mm. After several transfusions she made a complete recovery. The cause for the disturbed blood picture was not determined.

If we conceive of aplastic anemia as a depression of hematopoiesis in which all of the bone marrow elements are not simultaneously involved to the same degree, the case of Foderl,[30] in 1938, comes to mind. Pallor and weakness, but no bleeding tendencies, were noted in the latter part of her third pregnancy by the patient, who was 23 years old. The erythrocyte count was 2,400,000 per c.mm.; the hemoglobin, 35 per cent; the platelets, 250,000 per c.mm.; and the leucocyte count, 4,500 per c.mm., with 45 per cent polymorphonuclears and 48 per cent lymphocytes. Two transfusions were given, delivery was uneventful, and thereupon the maternal blood picture returned to normal. Foderl considered this a normocytic aplastic anemia, resistant to iron and liver, and responding to transfusions.

The case in the literature most closely paralleling ours is that reported by Nieuwenhuis in 1938.[31] Weakness, dyspnea, and slight epistaxis occurred for the first time during the seventh month of the first pregnancy of an 18½-year-old girl. The uterus was slightly larger than expected from the duration of pregnancy, and the possibility of intrauterine hemorrhage was suspected. Examination of the blood revealed: hemo-

globin 13 per cent; erythrocytes 870,000 per c.mm., with 12 reticulocytes per 1,000 erythrocytes; platelets 12,000 per c.mm.; and leucocytes 1,500 per c.mm., with 81.5 per cent polymorphonuclear leucocytes and 18.5 per cent lymphocytes. Aspiration revealed that the sternal marrow was very poor in cells, with no or at most little signs of activity. No response to therapy was obtained. Accordingly premature labor was induced, and a short-lived grossly normal fetus delivered. Four days later a second marrow aspiration was reported as cellular, and on the sixth postpartum day the hemoglobin level was 42 per cent. Convalescence thereafter was uneventful.

In their analysis of porphyrin excretion in aplastic anemia, Dobriner, Rhoads, and Hummel[32] describe six cases, of which one is germane to our subject. A 30-year-old housewife (Case 3) had a chronic aplastic anemia of ten years' duration, discovered when a severe toxemia of pregnancy ended with a miscarriage. At that time her hemoglobin was 27 per cent, but was built up over a period of time to 65 per cent. Following each of two succeeding pregnancies there occurred a severe exacerbation, with improvement after termination of the gravidity. This is the only case of chronic aplastic anemia in this series.

TABLE II

	AGE	STAGE OF PREGNANCY	OBSETERIC MANAGEMENT	OUTCOME	REMARKS
1. Ehrlich, 1888	21	First trimester	Abortion	Death	
2. Planchard, 1887	29	At term	Normal delivery	Death	Diagnosis questionable
3. Hanot and Legry, 1889	25	Second trimester	Miscarriage	Death	Diagnosis questionable
4. Ricca-Barberis, 1908	25	Puerperium	Normal delivery	Death	Sepsis
5. Hirschfeld, 1906	34	First trimester	Abortion	Death	Gangrenous endometritis
6. Hirschfeld, 1906	38	At term	Normal delivery	Death	Died 9 months post partum
7. Massary and Weil, 1908	21	First trimester	Uninterrupted	Death	Death due to heart failure
8. Jungmann, 1914	29	At term	Normal delivery	Recovery	Diagnosis questionable
9. Larrabee, 1925	30	First trimester	Uninterrupted	Death	No post mortem
10. Müller, 1938	28	Post partum	Normal delivery	Recovery	Several transfusions
11. Foderl, 1938	23	Third trimester	Normal delivery	Recovery	Several transfusions
12. Nieuwenhuis, 1938	18	Third trimester	Interrupted	Recovery	Severe case resembling ours
13. Dobriner et al., 1938	30	3 pregnancies	Interrupted	Recovery	Chronic with exacerbations
14. Hurwitt and Field, 1939	27	First trimester	Uninterrupted	Death	Failure of intense therapy

DISCUSSION

From the small number of case reports, it would appear that the occurrence of aplastic anemia during pregnancy is extremely unusual. Nevertheless it is important from the point of view of therapy to determine whether this occurrence is coincidental, or whether in these isolated instances the pregnancy itself may be an etiologic or precipitating

factor. A survey of the published cases of aplastic anemia in females reveals that the average age is in the thirties even though many children are included, whereas in the pregnant group the average age is in the twenties. However it must be recalled that the vast majority of pregnancies occur in the third decade.

Of greater significance is the fate of the aplastic anemia in terms of the course of the pregnancy. In this series of 14 cases, there were 9 deaths and 5 recoveries. The recoveries all took place after pregnancy had been terminated, either normally or by interference.

Among the 9 fatalities, there were 6 patients in whom the uterus had been emptied. Two died with septic complications. In two other cases, those of Planchard and of Hanot and Legry, the diagnosis of aplastic anemia lacked adequate necropsy confirmation. The inadequacy of the hematologic reports in the case of Hirschfeld, the patient dying nine months after delivery, makes analysis of his case difficult. The only clear-cut fatal case, therefore, after the uterus had been emptied of the products of conception, is that of Ehrlich, in which pregnancy had been unsuspected until curettage for uterine bleeding revealed shreds of fetal membranes.

There were only three cases in which the uterus had not been emptied; all three of these patients died. The spontaneous abortion in our case must be regarded as an agonal phenomenon. These three fatalities all occurred during the first trimester of pregnancy, at a time when interruption could most easily have been accomplished.

When we consider the five patients that recovered, the probable significance of the termination of pregnancy appears in an even stronger light. The case of Jungmann, of profound anemia discovered at term with prompt recovery in the puerperium, is not fully established as being one of aplastic anemia. However, the case of Müller, discovered post partum, ran the clinical and hematologic course of an aplastic anemia, with recovery after several transfusions. The remaining three cases were diagnosed while a state of pregnancy still existed. Foderl's patient received two transfusions, went through a normal delivery, and thereafter made an uneventful recovery.

The most convincing evidence that the occurrence of aplastic anemia during pregnancy may be more than mere coincidence is supplied by the case of Nieuwenhuis. The diagnosis of aplastic anemia in the presence of a seven months' gravidity was made clinically and hematologically, and confirmed by bone marrow aspiration. There was no response to any therapy until interruption of the pregnancy, when there was prompt clinical and hematologic improvement. This case differs from ours chiefly in occurring later in pregnancy, and the maintenance of a granulocytosis in the face of leucopenia. The case of Dobriner, Rhoads, and Hummel, with exacerbations during each of three pregnancies and prompt improvement following interruption, strongly suggests a causal relationship. It would be of interest to ascertain the course of subsequent possible pregnancies in these other four women who recovered.

From these considerations it would appear that the indication for the termination of pregnancy in the face of acute aplastic anemia is a most

pressing one. The situation at best is precarious; to procrastinate is to invite a fatal issue. Although interruption of pregnancy had been strongly considered in our case, it was felt that the patient's condition was at all times too poor to warrant interference. However it would appear probable from this review that her only chance for survival would depend on emptying the uterus as soon as she could be strengthened as much as possible. Although apparent clinical improvement may be slight, the blood level may be raised somewhat by transfusions. Certainly the failure of intensive conservative therapy in our case, with almost daily transfusions, as contrasted with the case of Nieuwenhuis, constitutes a most potent argument for advising termination of pregnancy.

In addition to the large groups of cases of anemia in pregnancy attributable to deficiency states or secondary to some manifest condition, sporadic instances are not wanting of profound anemias for which no adequate cause can be found, and which fail to respond to the usual therapy of iron, liver, and transfusions. Many of these recover following termination of the gravidity. An example of this type of case is that of ten Berge,[33] which concerned a 29-year-old woman who was found to have a severe anemia in the eighth month of pregnancy and who promptly recovered following the delivery of a macerated fetus.

Such instances, in addition to the aplastic group, have led many observers to postulate a possible pregnancy toxin as the responsible agent. Certainly such cases as the one above and that of Nieuwenhuis are most highly suggestive that some derangement of pregnancy may be present. The paucity of anatomic abnormalities in the mother and fetus in our case leads one to think of a possible etiology in other than structural terms.

It has been shown by Alice Hamilton in her analysis of benzene as an industrial hazard, that women are not only more susceptible to this substance than men, but that when pregnant they succumb to conditions to which they had previously been tolerant.[34] The case described by Dobriner, Rhoads, and Hummel[32] is an example in point. Their work on porphyrin excretion would indicate that primary aplastic anemia may result from an intoxication, in contrast to the groups of anemias attributable to deficiency states. Hurst has suggested that an endocrine imbalance may be the basis for idiopathic aplastic anemia.[35] An example of this is the occurrence of severe anemia of the aplastic type associated with sclerosis of the thyroid gland which was described by Jaffe.[36] The concept of a reciprocal maternal-fetal sensitizing effect, based on an antigen-antibody reaction, is raised by the work of Levine, Katzin, and Burnham on the possible bearing of iso-immunization in pregnancy to the etiology of erythroblastosis fetalis.[37] If we are to hypothecate a toxin, a hormonal imbalance, an immunologic change, or some other physiologic disturbance, we must realize that as yet there is no experimental evidence to establish these theories. Nevertheless the conclusion would appear warranted that rarely, during the complex bodily adjustments to a state of pregnancy, a combination of factors may arise predisposing to the development of an aplastic anemia, recovery from which sometimes follows termination of the pregnancy.

SUMMARY AND CONCLUSIONS

1. A case is presented of aplastic anemia occurring during pregnancy, with fatal issue; clinical, laboratory, and pathologic data are given.

2. Eighty cases of primary aplastic anemia in women were collected from the literature; 13 of these were found to be of obstetric significance.

3. Of the total group of 14 cases of aplastic anemia during pregnancy, there were only 5 survivals. In all of these the uterus had been emptied, 2 by normal delivery at term and 2 by interruption during the third trimester. One case developed post partum.

4. A fatality was recorded in each of the 3 cases in which there was no interruption of pregnancy.

5. From the evidence at hand it would appear probable that the occurrence of aplastic anemia during pregnancy may not be coincidental, but that the gravidity may play an etiologic or conditioning role.

6. Interruption of pregnancy should be strongly considered in the presence of aplastic anemia.

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SIMULTANEOUS RADIOLOGIC AND KINETIC RECORDING OF UTERINE AND TUBAL MOTILITY

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THE purpose of this communication is to describe a new technique for the simultaneous radiologic and kinetic study of uterine and tubal motility.

Transuterine insufflation of gas according to the method of Rubin has been employed for the clinical determination of tubal patency and the kymographic pressure tracing has been shown to throw light on certain endocrine levels of the patient. The mechanical factors for the various pressure complexes on these tracings have not been fully explained, and the technique here described may add something in this field.

The anatomic site involved in the complexes, and the nature of the observed muscle phenomena, present, as yet, unsolved fundamental problems. Previous studies have used a variety of approaches to these problems:

1. *In Vitro Experiments With Excised Tubes or Uteri.*—These experiments furnish information about *denervated* organs. In a previous communication,[1] we have shown the important effects of the extrinsic nerves upon insufflation tracings.

2. *Direct Visual or Photographic Studies With and Without a Window.*—This type of experiment is subject to the following possible criticisms:

a. The organs are small and observations are limited to the outer surface of the uterus and tube. The significant changes are in the luminal diameters of these organs. In rabbit insufflation we have seen rippling motions of the tube which are probably due to contractions of the smooth muscle in its mesentery without any obvious effect upon the luminal diameters as observed on the kymograph.

b. The motions are probably slow. In one human patient who was insufflated with the abdomen opened under procaine infiltration of the abdominal wall, we obtained a typical insufflation tracing but could not see any activity of either tube or uterus.

c. Artifacts are constantly being introduced by the motion of adjacent viscera.

3. *Resection of Portions of the Tube.*—Wimpfheimer and Feresten have shown that in rabbits[2] practically normal tracings could be obtained with most of the tube excised. They attributed the various complexes to the first portion of the extrauterine part of the tube. P. Schneider[3] claimed that his x-ray studies suggested that the intrauterine part of the tube was responsible. Obviously, the principle of partial resection furnishes only presumptive, not direct, evidence. In cardiac

physiology, the conduction system maintains the normal cardiac rhythm, and on removing it, a different rhythm is initiated which arises from cardiac musculature itself. Furthermore, the relative importance of the intrauterine and extrauterine portions of the tube is difficult to evaluate in rabbits because of the gradual merging of the two; their surgical division becomes a formidable technical problem.

4. *Radiographic Studies With Contrast Media.*—These have demonstrated peristaltic, antiperistaltic, and segmental contractions in the tubes and also the existence of what has been called a "cornual sphincter" in the intrauterine part of the tube. However, we have found no literature dealing with the correlation between x-ray pictures and simultaneous kinetic studies.

Previous observations on gas insufflation:

Technique of Gas Insufflation.—Gas, usually carbon dioxide, is passed from a tank with a pressure head of 760 mm. Hg through a reducing valve, so that flow is about 30 to 100 c.c. a minute through a cannula placed in the cervix. A recording manometer of the brass anaeroid or mercury-float type is incorporated in the apparatus to register the pressure during the insufflation. Usually there is also some device, such as a flow meter, to indicate volume flow of gas.

Type of Pressure Curve Obstained.—In human beings and rabbits similar curves have been obtained. There is a primary pressure peak, *A*, which is usually the maximum pressure reached before gas enters the abdomen. The pressure then falls to a level, *B*, the so-called plateau level, which persists throughout the course of several minutes of insufflation. Upon this plateau level are superimposed major C and minor D waves of pressure.

1. The kymographic tracing is essentially a record of perfusion pressure obtained when gas is passed through a hollow system of changing caliber. In studying the behavior of any smooth musceled viscus, the usual stimulus is distention and the response is measured in terms of pressure. In the case of a closed organ, as for instance the urinary bladder (assuming no ureteral reflux), the pressure response to different degrees of volume distention and any resultant rhythmic activity can be recorded easily on any simple manometer. In the case of the uterus and tube, the abdominal ostium permits escape of stimulating media. *This requires a constantly renewed stimulus.*

2. Among the various mechanical factors involved in the study of perfusion pressures are:

a. *Viscosity of Medium:* Gas has low viscosity and the use of fluid as a perfusing medium demands distinct compensations in technique, especially rate of flow. Early experimental attempts to use fluid, frequently resulted in rupture of the thin-walled rabbit uterus because the flow of fluid was not reduced sufficiently to compensate for its high viscosity.

b. *Rate of Flow:* In an inelastic system, the pressure varies directly with the flow. In a previous communication,[4] we have shown the marked kymographic differences obtained on altering the rate of gas flow. It is true that the organs, in time, tend to compensate to some extent for these changes and preserve a relatively constant pressure.

c. *Total Capacity of System:* For similar flow rates, the pressure varies inversely with the size of the system. Compensations must be

made in animal insufflations for the smaller size of their organs. Furthermore, changes in intra-abdominal pressure directly affect the capacities of these thin-walled, easily compressible organs.

d. *Local Changes in Resistance:* Pressure varies inversely with the square of the radius. In the case of the uterus and tubes, the tube presents the smaller luminal diameter, and small linear changes in its diameter produce greater pressure effects. Contractions of the tube may be one of several observed types, segmental, peristaltic, or antiperistaltic. In the case of rhythmic segmental contractions, the pressure level rises proportionately to the decrease in luminal diameter and over a period of time depending on the duration of the contraction. The duration of contraction is very important and must be correlated with the rate of flow of the perfusing medium. The observed minor waves

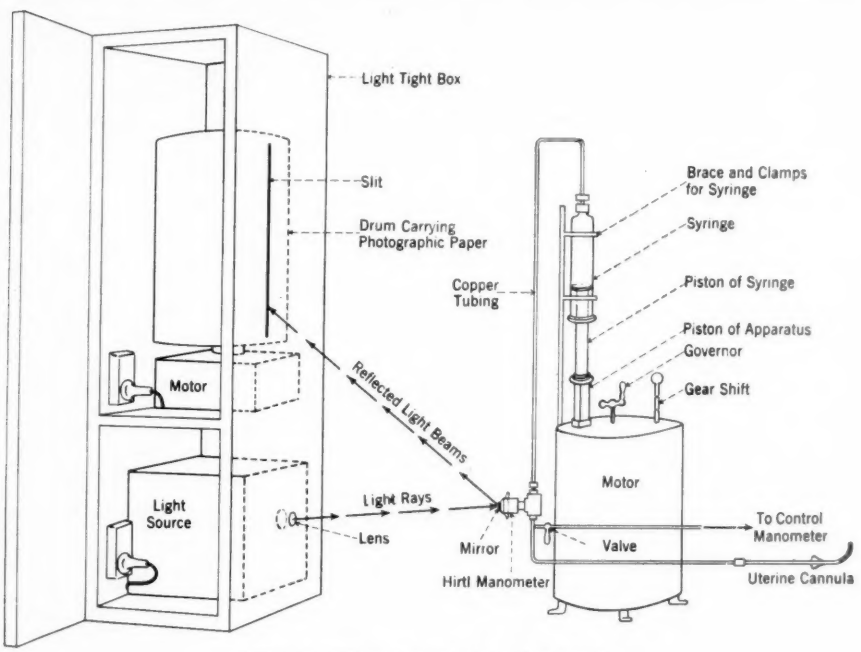

Fig. 1.—Diagram of apparatus used.

of pressure during gas insufflation do not imply that complete closure of the lumen occurs at each rise in pressure. At slow rates of gas flow (30 to 40 c.c. a minute in rabbit investigations), complete closure is probable, for no gas escapes from the fimbriated end of the tube during the rises in pressure. At more rapid rates, gas may escape continuously even though rhythmic pressure oscillations are recorded. The slope of the rise of pressure is an index of the extent of closure. The effect of a peristaltic wave on the recorded pressure is contingent on both the extent of contraction and the speed of the wave. If a propulsive peristaltic wave moving from the uterus to the fimbriated end of the tube carries away a column of medium faster than it is being delivered, the pressure in the system will fall. Slower waves and all waves moving toward the uterus would cause a rise in pressure.

DESCRIPTION OF NEW APPARATUS

1. Perfusing medium: Fluid is used because it is not compressible and its kinetics are easier to interpret than those of gas flowing at a slow rate. Moreover, it can be rendered radiopaque and is a medium of low viscosity. Hippuran (aqueous) was chosen in preference to the more opaque but viscous oily solutions used clinically. Lipiodol would have given better contrasting pictures, but its viscosity produces considerable lag.

2. Constant delivery of the medium is provided by a motor-driven syringe. The rate of flow in this specially devised apparatus can be regulated within a range of 0.1 to 1 c.c. and quick changes in rate are possible by the use of a gear system, like an auto gear shift. The motor driving the syringe is of the synchronous motor type which moves the syringe a unit distance independent of load, until a pressure is generated which exceeds 30 pounds (beyond the working range of these experi-

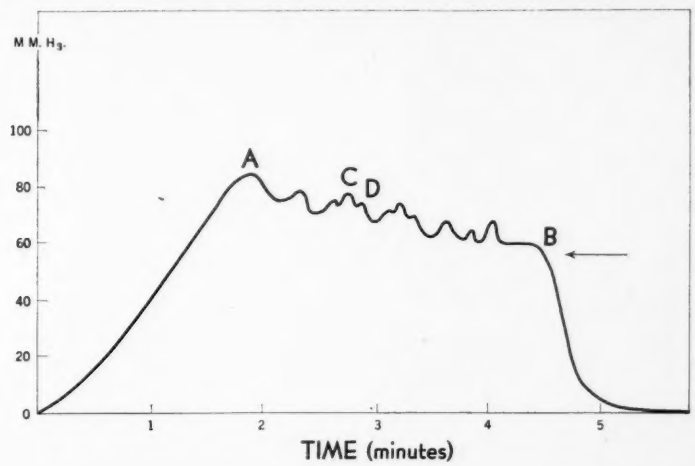

Fig. 2.—Showing typical inflation curve. *A*, Initial rise of pressure. *B*, Pressure plateau. *C*, Major contractions. *D*, Minor contractions.

ments), at which point the motor is arranged to stall. All tubing is of copper. In the clinical gas insufflation apparatus, the flow is not constant enough for this investigative work. In that type of apparatus, the flow is dependent upon the pressure differential between the source of 760 mm. Hg and the working range 0-200 mm. Hg, permitting variations in flow of more than 25 per cent. Furthermore, expansile tubing is used, with its obvious limitations.

3. Continuous pressure records were obtained through a simplified optical manometer incorporated in the system. Inasmuch as the delivery rate is slow and the pressure variations small (0-5 mm. in the minor waves), a sensitive manometer which requires very slight displacements of fluid for recording purposes is of great advantage. The figures comparing the gas-anaeroid system and our fluid-optical drum are

	GAS	FLUID
R—Rate of flow per minute	30 c.c.	0.1 c.c. — 1 c.c.
V—Volume of medium needed to fill manometer to produce a record of 200 mm. Hg	40 c.c.	0.06 c.c.
Ratio of R/V	0.75	1.66 — 16.6

The apparatus is fully sensitive enough to pick up human pulse tracings.

4. Serial x-rays are synchronized to the inflation apparatus, and are taken by means of a continuous strip of radiosensitive paper passed from one lead-lined chamber, crossing under a radiotransparent bakelite window into a lead-lined receiving chamber. The paper is moved along by a hand-driven rubber-covered cylinder and 40 pictures can be taken a minute, allowing 0.3 second intervals for actual exposure time. Appropriate markers on the recording camera indicate the radiograph taken. No such elaborate apparatus was at this time available for our studies in human beings.

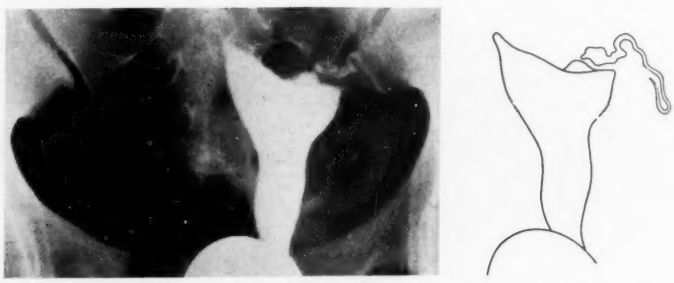

Fig. 3.—Normal uterus and tubes; three months post-partum. Medium passing left tube. Isthmic contractions. At this time the pressure was rising and rhythmic waves were registered on the manometer.

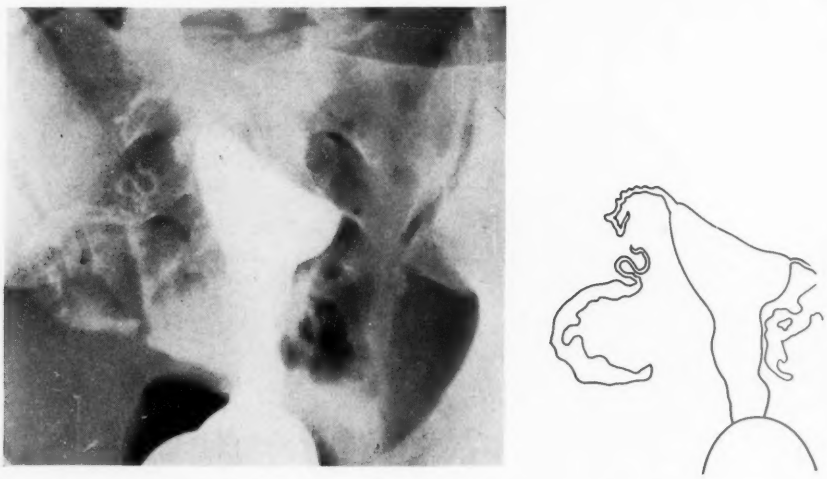

Fig. 4.—Same case. Fluid freely passing both tubes. At this time, pressure waves disappeared.

CLINICAL OBSERVATIONS

1. In two patients who had normal parturition two months previously, no fluid could be driven past the tubes within safe limits of pressure (never exceeding 200 mm.). In each case, however, rhythmic uterine contractions were recorded while the uterus was being distended with fluid. In each case, the x-ray showed the typical funneling at the cornual angle, and the apparent block at the beginning or in the first part of the isthmic portion of the tube.

2. In one patient, who was three months post partum, we obtained a pressure tracing with rhythmic pressure waves of a range of 10 mm. Hg

for a few minutes. An x-ray obtained while the pressure was rising during these waves, revealed the left tube filled with medium, with the exception of the first centimeter of the isthmic portion. This would suggest a tubal contraction in the isthmus. The waves of pressure then disappeared completely, and the plateau level of insufflation pressure fell. An x-ray at this time showed that fluid was pouring through a completely filled right tube, and the left tube was partially filled in its

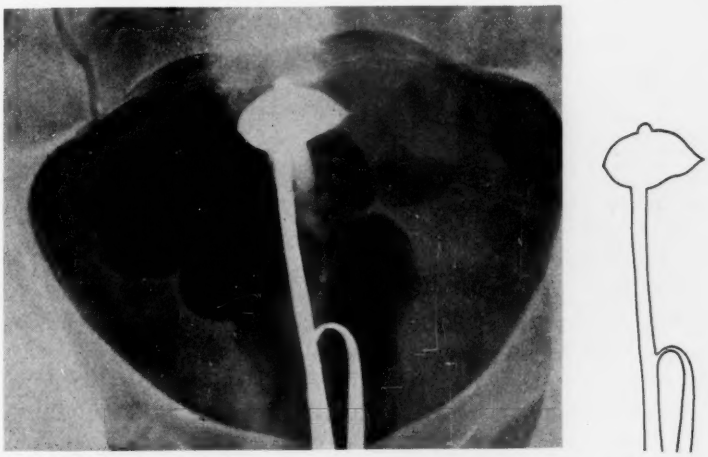

Fig. 5.—The tube removed for ectopic pregnancy. Fluid in ampulla and in pelvis; none in the isthmic portion during waves of tubal contraction.

Fig. 6.—Normal post-partum uterus. No fluid entering tubes. Visualization of isthmic portion. Terminal regurgitation.

ampullary portion. This would tend to support our previous contention that the usual type of insufflation tracing with small waves of pressure was probably obtained through gas passing through a single tube, rather than both tubes.

3. In two patients with single tubes (the other tubes having been removed for ectopic pregnancies), gas insufflation revealed normal tracings. In these cases, rhythmic waves of pressure were observed

when the fluid passed through the tubes. In both, the rises of pressure were associated with either completely empty tubes, or with medium only in the ampullary portions.

We have performed experiments on numerous rabbits and found the technique feasible. Inasmuch as the Fallopian tubes in the rabbit are extremely narrow, it was necessary to draw them out of the body and place them on a special x-ray table. We are fully aware that the unavoidable displacement of the tubes for the sake of obtaining our visual records introduces a factor which is subject to the criticism of being unphysiologic.

CONCLUSIONS

1. A technique for simultaneous kinetic and radiologic studies on uterine and tubal motility has been described. It should be noted that the need for meticulous control of all factors makes this method, as used at present, a strictly investigative procedure. For instance, the very fact that we are studying a single closed constant perfusion system would invalidate experiments in the event both tubes were patent. Thus, of necessity, we have been restricted in our investigations to cases in which one tube has been removed, i.e., for ectopic pregnancy, and in which the residual tube has been found normal by all available standards.

2. In insufflation of gas or fluid in human beings, the fluctuating waves of pressure are probably isthmic in origin.

We are indebted to Dr. A. Unger, radiologist at Sydenham Hospital, for his invaluable cooperation. We wish to thank the Johnson Research Foundation for their assistance in the acquisition of our apparatus, and Mr. Descoteau for his technical help.

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Some noteworthy figures are quoted: 79 women, considered in this study, had 1,556 pregnancies, of which 869 terminated in viable births, 212 in spontaneous, and 475 in induced abortions. In terms of percentages, only 55.8 per cent of all conceptions reached viability, 13.6 per cent ended in spontaneous, and 30.5 per cent in induced abortions. Out of 979 women, 636 became pregnant (65 per cent), and 63.8 per cent experienced at least one abortion (spontaneous or induced) which makes 1.7 abortions for each woman. It was found that 90 per cent of these women had married before the age of 30. The largest number of abortions, both spontaneous and induced, occurred during the second month of gestation. The first two pregnancies were most likely to be carried to term. With each subsequent conception the chances of survival for the fetus were sharply reduced. It was also found that the overwhelming number of induced abortions were done by physicians and by means of instruments.

WILLIAM BERMAN.

CHORIONEPITHELIOMA*

A Study of Thirteen Cases

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PROBABLY no rare tumor exhibits such markedly malignant characteristics as chorionepithelioma. While the number of reported cases is fairly small in comparison to other malignancies of the female genital tract, their occurrence is common enough and the malignant potentialities so great, as to warrant special attention.

During the years 1925 to 1940 inclusive, 2,042 patients with malignancy of the female genital tract were seen in the Gynecology Clinic of the University of Michigan Hospital. A diagnosis of chorionepithelioma was made in 13 patients, an incidence of 0.63 per cent.

PARITY

The disease occurred twice in primigravidas and eleven times in multiparous patients, coinciding with the majority of reports that chorionepithelioma usually occurs in multiparas. The average parity of the entire group was 2.2 full-term pregnancies. The average gravidity was 3.2 pregnancies. The relation of parity is only of academic interest since multiparas far outnumber primiparas.

AGE

While most other malignant diseases of the female genital tract usually occur during or near the menopause, chorionepitheliomas occur almost entirely during the childbearing period. Our oldest patient was thirty-nine, the youngest nineteen years of age. The average age of the entire group was 28.2 years. Teacher,[1] in his review of 188 cases, claimed that the incidence of chorionepithelioma reaches its peak at the age of 33.

There was one colored patient in our series, the remaining twelve were white.

There exists considerable controversy among the leading authorities regarding the etiology of chorionepithelioma. Most statements propose a possible cause but really offer nothing more than a discussion of the nature of its precursor. Since the cause is still unknown, most of the literature on this point can be summarized by stating that the presence of living chorionic tissue in any location is potentially malignant. Except for the very rare situation wherein chorionepithelioma occurs in a primary tumor of the ovary or in a teratoma, most cases follow moles, abortions, term pregnancies and ectopic pregnancies, and in that order.

Findley[2] in a report of 500 collected cases of hydatidiform mole found that 157, or 31 per cent, developed chorionepithelioma. Although a sum-

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mary of the world literature by Mathieu[3] in 1939 revealed that 10 per cent of moles develop into chorionepithelioma, Mathieu concluded that 50 per cent of chorionepitheliomas are preceded by the passage of moles, the others developing after full-term pregnancies and abortions with emphasis on the latter.

The stress placed on the development of chorionepithelioma following the passage of a mole or an abortion indicates more than the casual interest so frequently displayed in the management of these conditions. The precursor of chorionepithelioma in our series, as compared with that of other authors, is recorded in Table I.

TABLE I. ANTECEDENT CONDITION

	MOLE	ABORTION	FULL TERM	ECTOPIC	UNKNOWN
Schumann[4] (15)	8	0	0	0	7
Teacher[1] (188)	73	59	53	3	0
Mahfouz[5] (15)	8	5	1	0	1
Brews[6] (24)	8	7	4	0	5
Mathieu[8] (28)	15 5 associated	7	1 associated	0	0
U. of M. (13)	5	5	3	0	0
Wilson[7] (5)	2	2	0	0	1 (mole 2 yr. before; pregnancy 1 yr. before)

In our series, the average length of time between the occurrence of the predisposing condition and the diagnosis of chorionepithelioma was nineteen months. The longest interval was nine years, following a full-term pregnancy. The shortest interval was ten days, following the delivery of a full-term pregnancy. However, further investigation and analysis of the former's history revealed irregular periods of two years' duration, each mensis lasting from five to seven weeks with continuous bleeding for the five months prior to admittance to this hospital. Excepting this case, the longest interval between the appearance of the precursor and the chorionepithelioma was twenty-seven months.

SYMPTOMS

The most characteristic and important symptom of chorionepithelioma is vaginal bleeding. This bleeding may occur shortly after the termination of pregnancy, whether it be a full-term pregnancy, mole, or an abortion, and is due to the corrosive action of the trophoblast on the walls of blood vessels. The latent period may be from several weeks to several months. The bleeding is scant in most cases, gradually increasing in amount as the condition progresses. It is not altogether improbable that bleeding may have existed and then stopped, where the tumor had been totally intramural. The early signs and symptoms are not characteristic and frequently simulate those associated with retained membranes, sepsis and/or involution. The bleeding may be irregular, sudden, severe, or depleting, or the patient may have just a mild amount of serous or serosanguineous discharge.

In Mathieu's[8] series of 28 cases collected from the entire Pacific Coast region between the years 1931 and 1936, the most frequently noted

symptoms were vaginal bleeding, nausea and vomiting, painful uterine contraction, or no symptoms whatsoever. In our group of cases, vaginal bleeding was the first symptom in 10 patients and chest pain, hemoptysis, and central nervous system symptoms occurred in one of each of the three remaining patients. The cerebral symptoms were headache and blurring of vision. The average duration of symptoms in our group before a diagnosis was made was 6.2 months. The shortest duration of symptoms was three weeks in the patient with cerebral symptoms, the longest duration being twelve months in a patient who had vaginal bleeding following an abortion at three months of gestation. Bleeding following curettement in an incomplete abortion should make the observer suspicious of the possibility of chorionepithelioma. Often, the curette is unable to obtain deep-seated myometrial implants of chorionepithelioma, but even in those where tissue can be obtained, mistakes are frequently made in the microscopic interpretation of the tissue. According to Teacher, it is sometimes very difficult or even impossible to draw a sharp histologic distinction between the villi of simple hydatidiform mole and those of chorionepithelioma. In Schumann's study of 15 cases, he reports one case where the Aschheim-Zondek test was negative and curettings revealed only deciduitis.

Pain as a symptom does not occur until late in the disease. Anemia from acute or chronic hemorrhage may be prominent. Low grade fever, probably on the basis of bacterial invasion of secundines remaining in the uterus, is not uncommon and frank sepsis may be present. The cause of this fever must also be differentiated from secondary pneumonic disease, cerebral processes, from primary incomplete infected abortion, as well as other common causes of fever.

DIAGNOSIS

Prior to the development of the Aschheim-Zondek test in 1928, the diagnosis of chorionepithelioma depended upon the presence of profuse or continuous uterine bleeding, the microscopic appearance of curettings, and the presence or absence of remote metastases. Between the years of 1932 and 1940, the Aschheim-Zondek reaction was utilized in the last 8 cases of chorionepithelioma diagnosed in our clinic. In all 8 patients the Aschheim-Zondek reaction was positive. After admittance to the hospital, the diagnosis was made in all patients in less than ten days after initial admittance. Dilutions of urine were run for the determination of gonadotropic substance on several of the patients and are recorded in Table II.

TABLE II. ASCHHEIM-ZONDEK REACTION

NO. OF CASES	UNDILUTED	1:50	1:100	1:200	1:2000
3	+	0	0	0	0
1	+	+	0	0	0
2	+	+	+	0	0
1	+	+	+	+	0
1	+	+	+	+	+

The value of the Aschheim-Zondek test cannot be too strongly emphasized in dormant cases of chorionepithelioma. It is just as important in the diagnosis of chorionepithelioma as the Kahn test is in the diagnosis

of syphilis. Since mistakes are frequently made in the microscopic diagnosis of the disease, the Aschheim-Zondek test should serve to confirm the microscopic and clinical findings. The biologic test is more accurate than histologic diagnosis on the basis of tissue study. Because of this, considerable skepticism has arisen regarding the true diagnosis of cases so diagnosed before the advent of the test. The biologic test should be utilized in every suspected case in conjunction with clinical examination and the use of other methods which contribute toward making the diagnosis. The concentration of the gonadotropic substance in the urine is not necessarily an important factor in determining the presence or absence of chorionepithelioma, since, in a recent study of women who were seen with normal early pregnancies, positive reactions from these patients' urine, diluted 1:200, were obtained. We feel that any patient who persists in bleeding following a curettage for incomplete abortion or following the evacuation or passage of a mole should be followed by periodic biologic studies. The presence of a positive reaction six weeks after a curettement or passage of a mole should be considered diagnostic of chorionepithelioma. The reaction obtained in the Aschheim-Zondek determination is practically never weak if retained chorion is present. There may, however, be a long latent period of negativity during which time a previously passed molar pregnancy may develop into chorionepithelioma. It is therefore important that frequently repeated tests be carried out in order to make early diagnosis possible. The diagnosis of chorionepithelioma after the appearance of metastases is easy.

Since error in diagnosis may be fatal, more frequent use of the Aschheim-Zondek test is indicated in patients presenting a suspicious abnormality. We prefer the Aschheim-Zondek test, using five mice, rather than the Friedman test with one rabbit, since the chance of detecting early changes is greater. If the mice are killed by the high concentration of gonadotrope or toxic substance in the urine, we favor the repetition of the tests with more dilute specimens.

TREATMENT

Practically all authors agree that once chorionepithelioma has been diagnosed, the proper treatment is immediate hysterectomy. Most observers agree that early diagnosis and adequate early treatment offer the best prospect for cure. Some authors favor subtotal hysterectomy. It is our feeling, however, that if the patient presents even localized malignancy in the uterine wall, the possibility of hematogenous metastases is omnipresent, and for this reason a more radical attack is necessary in order to be certain that all of the neoplasm has been eradicated. We feel that a cure of chorionepithelioma, in the operable case, is based upon total hysterectomy, plus removal of both tubes and ovaries. Preservation of the tubes and ovaries at the time of operation is favored by some, while some gynecologists are influenced in their decision by the presence or absence of ovarian involvement by the primary growth.

If blood loss has been excessive, it should be replaced preoperatively.

TABLE III. METHOD OF TREATMENT

	TOTAL HYSTEREC-TOMY	SUBTOTAL HYSTEREC-TOMY	REMOVAL OF VAG. IMPLANT	X-RAY THERAPY	NONE
Mathieu (28)	24	3	1	0	0
U. of M. (13)	6	0	0	4	3
Wilson (5)	2	1	0	0	2

In our cases, total hysterectomy and bilateral salpingo-oophorectomy were performed in six. The remaining 7 patients were inoperable; 4 were treated by x-ray therapy applied to the local lesion and metastases, while 3 patients received no treatment.

One of the advanced patients was admitted on the Neuro-Surgical Service with all of the characteristic signs and symptoms of brain tumor; the diagnosis was first made at the time of microscopic examination of tissue removed at time of craniotomy. One patient in our clinic who had had a total hysterectomy and a bilateral salpingo-oophorectomy for chorionepithelioma without demonstrable evidence of remote metastases was later admitted to another hospital with the diagnosis of meningovascular meningitis, and died within three days after her admittance. We can conclude, from these treated patients and untreated patients, that routine x-ray study of the chest and routine neurologic examination, along with gynecologic clinical and biologic investigation, should be performed in every suspected chorionepithelioma.

MORTALITY

Four of the 13 patients are living and well at the present time; all four of these patients were treated surgically by total hysterectomy and bilateral salpingo-oophorectomy. One of the 6 patients treated in this manner died of metastatic neoplasm two months postoperatively, and one fatality occurred as a result of acute intestinal obstruction. All of the patients with advanced cases treated by other methods, including irradiation, are dead.

TABLE IV. MORTALITY

	DEATHS	LIVING
Mathieu (28)	2	26
Brews (24)	14	10
Mahfouz (15)	3	12
U. of M. (13)	9	4
Wilson (5)	3	2

A summary of the mortality by various observers is recorded in Table IV. The survival percentages appear to be unusually high in some of the series. This information immediately raises the question of whether very early diagnosis was made in many of these cases or just how accurate was diagnosis. This point is well presented in Wilson's excellent report of 5 well-worked-up cases. In the collected series reported by Mathieu and in Mahfouz' series of 15 cases, the diagnosis was frequently made by microscopic examination of tissue only.

The interval between the time of admittance, when the diagnosis was made, and the time of death varied from one week to three months. The average interval was 1.1 months. The average interval between the date of the first symptom and the time of death was 5.7 months, with the shortest interval being three months and the longest interval fifteen months. Doubtless lives could be saved by general recognition of the fact that an early diagnosis of chorionepithelioma can be made only by careful consideration of vaginal bleeding following a pre-existing pregnancy, abortion, or mole.

The anatomic cause of death in our patients is listed in Table V.

TABLE V. MORTALITY

CAUSE OF DEATH	NUMBER OF CASES
Cerebral metastases	3
Diffuse meningeal involvement?	
Pneumonia, secondary to metastases	3
Cachexia	1
Intestinal obstruction	1

The sites of metastasis are listed in Table VI.

TABLE VI. METASTASES (NINE CASES, EIGHTEEN SITES)

SITES OF METASTASIS	NUMBER OF PATIENTS WITH THESE SITES
Lungs	5
Vagina	4
Brain	2
Liver	2
Rectum	1
Ovary	1
Diaphragm	1
Adrenals	1
Periaortic nodes	1

These sites of metastasis were found either at the time of operation, at autopsy, by roentgenographic examination, or by biopsy.

Pulmonary metastases occur by direct hematogenous embolic transmission. The mechanism of spread from the primary uterine site to the vagina most likely occurs by way of the fine interlacing of vessels between the fundus and cervix, and thence through the network of vessels common to the cervix and vagina. It is not altogether improbable that vaginal spread might also occur by systemic route in an embolic manner. Cerebral metastases, we feel, occur directly if a patent foramen ovale can be shown to be present. If this cannot be demonstrated, retrograde venous metastases, and tertiary spread from pulmonary metastatic lesions offer the more plausible explanations for this involvement. The remaining sites of metastasis occur by way of direct blood stream routes.

Lutein cysts were found in four of the patients, either at the time of autopsy or at the time of operation. In one patient in whom orange-sized lutein cysts of the ovary were found, the fluid from the cyst was studied to determine the presence or absence of gonadotropic substance,

The tests were very strongly positive. Lutein cysts did not occur with the same frequency in our group of cases as has been reported by other observers.

SUMMARY

We believe that early diagnosis of chorionepithelioma can be made only by constantly keeping the diagnosis in mind.

Of what significance is the biologic test in diagnosis? Any patient showing a positive biologic test for the luteinizing hormone four weeks after delivery of a full-term pregnancy or following an abortion, or, in whom the test remains positive for six weeks or longer following the passage of a mole presents strong evidence of an existing chorionepithelioma. While we have come to rely upon the reaction of the Aschheim-Zondek test, this test, plus clinical judgment, the evaluation of a complete history and microscopic appearance of the curettings should be used collectively rather than any one single criterion diagnosing the disease. Particularly significant is clinical judgment in evaluating the patient whose Aschheim-Zondek reaction becomes positive due to subsequent pregnancy.

What is the treatment of chorionepithelioma and what is the best way to treat this disease? On the basis of our report and of previous reports, we feel, at the present time, that these patients, if operable, are best treated surgically by the performance of a total hysterectomy and bilateral salpingo-oophorectomy.

Of what value is irradiation in the treatment of chorionepithelioma? We feel that, if diagnosis is made early enough to treat adequately these patients, surgery is the one treatment which will uniformly give satisfactory results. However, in the presence of metastases, the disease is best treated, and then probably only palliatively, by irradiation of the primary site and of the metastatic area, rather than by removal of the primary lesion in the hope that secondary metastases will disappear. The indications for surgery in this group should be limited to patients where continued and potentially fatal hemorrhage is present, as described by Wilson.

Frequent subsequent checks on operated patients' urine for gonadotropic substance should be carried out at monthly intervals during the first postoperative year, and once every two months during the second year. Where circumstances permit, it would be desirable to check these patients clinically and biologically at least twice yearly throughout life.

Routine roentgenographic examination of the chest and neurologic examination are indicated prior to operation in all patients suspected of having chorionepithelioma.

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GYNECOLOGIC TUBERCULOSIS

A Brief Review of Thirty-Two Cases, Including One of Tuberculous Cervicitis

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GENITAL tuberculosis was first recognized by Morgagni while performing an autopsy on a girl of twenty years. There were no other reports until those of Raymond, Reynaud, and Senn in 1831. Koch discovered the tubercle bacillus in 1882. In the following year Cornil and Babes first demonstrated the bacilli in the vaginal discharge. Since then, a voluminous literature has grown, slowly clarifying the various issues of pathology, diagnosis, and treatment.

Gynecologic tuberculosis may be a primary infection introduced by the male. Secondary infection by the hematogenous or lymphatic routes, or by direct extension from a neighboring organ, is the more frequent. Recent experimental work has demonstrated that re-infection through the vaginal route in a previously sensitized individual can produce typical clinical gynecologic tuberculosis. All organs of the female genitals have been known to be involved. The individual lesions vary greatly in their frequency, tuberculous salpingitis being the most common. Tuberculous vaginitis and oophoritis, the occurrence of which was denied until recently, are the least common.

Gynecologic tuberculous lesions vary greatly in type. Vulvar lesions are ulcerative, scrofulodermal or lupus-like. Cervical tuberculosis, which often looks like malignancy,[1] is catarrhal, miliary, ulcerative, vegetating, or interstitial. Corporeal involvement may be miliary, ulcerocaseous, hypertrophic or interstitial, and is frequently diagnosed wrongly as adenomyosis or fibromyomatosis because of the irregular contour of the tender uterus. These patients, as a rule, show advanced endometrial and tubal infection, and other evidence of tuberculosis is usually present. Tuberculous oophoritis is diagnosed only by the pathologist. Tuberculous salpingitis is protean in its nature, and may be miliary, nodular, atrophic, hypertrophic, or caseous.

It is currently agreed that genital tuberculosis is not diagnosed preoperatively unless it has been suspected. Pathologically, no diagnosis should be considered as certain until the tubercle bacilli have been demonstrated by any of the acceptable methods.

MATERIAL

From 1916 to 1940 inclusive, 1,600 autopsies and over 38,000 surgical specimens have been reviewed by the Department of Pathology at Mount Sinai Hospital in Cleveland. Thirty-two proved cases of gynecologic tuberculosis have been found. Six were verified at necropsy, and the

remainder had 30 gynecologic procedures by 12 operators. Patients with tuberculous skin lesions, peritonitis, perimetritis, perisalpingitis, or perioophoritis have been excluded, as have all those where no tubercle bacilli were found in the specimens after staining by the Ziehl-Neelsen method or by guinea pig inoculation.

The youngest patient in this series died of tuberculous meningitis at the age of two. Tuberculous salpingitis was an incidental finding at autopsy. The oldest patient was sixty-two years of age. The preoperative diagnosis of cervical malignancy was changed postoperatively to tuberculous vaginitis and endometritis. The average age of the entire group was 34 years. One patient was found to have tuberculous salpingitis sixteen years after tuberculous endometritis had been diagnosed by examination of the curettings. Tubal involvement was bilateral in all but one case, whereas oophoritis was always unilateral. Since complete operative procedures were done infrequently, it is difficult to determine the true incidence of organs involved. Vaginal procedures varied from dilatation and curettage to total hysterectomy and bilateral salpingo-oophorectomy. One Watkins' interposition operation and four gyneplastic repairs were included among the vaginal procedures. Abdominally, the most radical operation was a total hysterectomy, bilateral salpingo-oophorectomy and subtotal cystectomy in a patient with uterine malignancy and incidental tuberculous salpingitis. In one patient, the operation was limited to a biopsy of the involved tissues.

The organ frequency in the specimens examined by our laboratories was:

ORGAN	SURGICAL	AUTOPSY
Tubes (unilateral once)	23	6
Endometrium	9	1
Myometrium	5	1
Ovary (always unilateral)	3	0
Endocervix	2	1
Cervix (interstitial)	1	0
Vagina	1	0
Vulva and Bartholin gland	0	0

Reports in the literature state that tuberculous cervicitis occurs about once to every 200 cervical malignancies. During this same interval, our pathologists diagnosed 201 carcinomas of the cervix uteri.

The diagnosis was made preoperatively in only 3 patients, all of whom gave a history of previous tuberculous peritonitis. Diagnosis was made at operation in 13 cases. Four patients were parous, one having borne eight children. Eight were unmarried. The preoperative diagnosis in 3 of these was ectopic pregnancy. In one, who had a tender pelvic mass and an amenorrhea of five months, the Friedman test was weakly positive. The final diagnosis was tuberculous pyosalpingitis. This was the only patient in the entire series who had missed any periods, though all but 5 complained of menstrual irregularities. Menorrhagia, with or without metrorrhagia, and associated with severe dysmenorrhea occurred in the majority. Except in those with pelvic abscesses, the disease was never suspected.

The incisions of 11 patients were not healed and still draining at the time of their discharge from the hospital. Drainage had been instituted at operation in 5 patients, and the wounds of all broke down. Two incisions were resutured, but disrupted a second time. One patient developed a rectovaginal fistula after the removal of a left tuberculous tuboovarian mass. One patient, at necropsy, was found to have a sigmoidosalpingovesical sinus which communicated with a tuberculous pelvic abcess. Death followed uremia secondary to tuberculous destruction of both kidneys. One patient developed an acute tuberculous peritonitis after her operation but recovered. One patient died within a month of her delivery of a normal term infant.

A slight to severe anemia was present in 22 of the 30 surgical cases. Nine required transfusion for blood loss during the operation or for postoperative shock and sepsis. The white blood count on admission was elevated above 10,000 per c.mm. in sixteen patients. The highest count was 23,500 in a patient with pelvic abscess. No sedimentation rates were done. Nine patients were discharged before the fifteenth postoperative day. The average hospital stay was 25.3 postoperative days, and the longest was 85 days.

Two patients later developed malignancy. The first patient died of an alveolar adenocarcinoma of the lung with generalized metastases two years after the internal genitals had been removed for tuberculosis and fibromyomas. The other, in whom a diagnosis of tuberculous endometritis had been made sixteen years previously, was operated upon for uterocervical malignancy which involved the bladder. An active tuberculous salpingitis was found at this time. She is still alive three years after this second procedure.

Seven patients were not seen again after their discharge from the hospital, and 6 were followed for less than one year. Of the others, 6 are apparently free of tuberculosis at present. Two are inmates of sanitoria. One has pulmonary tuberculosis, and the other is recovering from tuberculous peritonitis. One patient has a laryngeal lesion which is suspected of being tuberculous. Four patients are known to have died, one of drowning, one of generalized tuberculosis, and one of carcinoma of the lung. In the fourth patient, the cause of death is unknown.

Of the 6 patients in whom autopsy confirmed the diagnosis, 2 died of uremia and pyelonephritis. One, the youngest, died of tuberculous meningitis. The fourth developed a pleurisy with effusion in the fifth month of pregnancy, delivered normally at term and came to necropsy four weeks later with an acute generalized miliary tuberculosis. The last two were classified as anesthetic deaths, dying under anesthesia for tooth extraction and cholecystectomy, respectively. The findings of gynecologic tuberculosis were incidental in each of these.

CASE REPORT

A detailed report of the most recent patient follows: A. D. (S. P. No. 35207 and 35298), negress, aged 18 years, was admitted to the gynecological service at Mount Sinai Hospital on Sept. 12, 1939. She complained of acute generalized abdominal pain associated with nausea,

colic, and occasional emesis of twenty-four hours' duration. The onset followed cessation of her last menstrual period on Sept. 10, 1939. Menarche occurred at fourteen years of age, and menses had always been regular, lasting three to four days. They were occasionally associated with lower abdominal cramps during the first day of flow. There had been a moderate leucorrhea for the past year. Promiscuity without prophylactics was admitted.

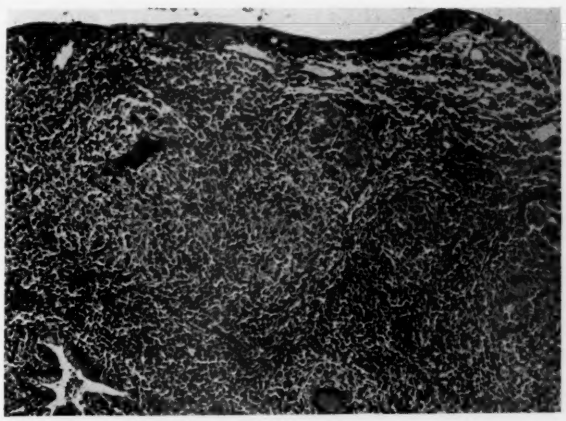

Fig. 1-*A*.—(S. P. No. 35298.) Tuberculous cervicitis. The surface is denuded. A cervical gland is seen at the lower left corner. The remaining tissue is not recognizable. There are areas of degeneration, tubercle formation and several typical Langhans' giant cells.

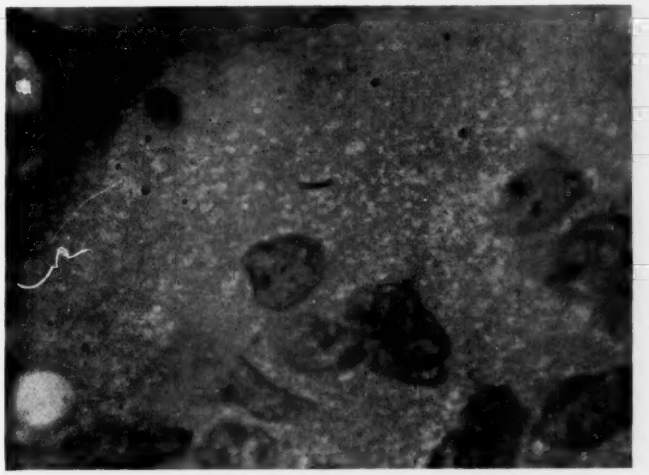

Fig. 1-*B*.—Ziehl-Neelsen stain showing a tubercle bacillus in one of the giant cells in Fig. 1-*A*.

Past history at the time of admittance was noncontributory. Later, it was learned that she had had a pleurisy with effusion in 1937. Family history showed that her sister died of pulmonary tuberculosis in 1936. At that time the patient's von Pirquet test was positive, but x-ray of the chest was reported as negative. Temperature on admission was normal, but rose to 101° F. Pulse was 110 per minute; hemoglobin,

85 per cent; the red and white counts were 4.5M and 11,400 per c.mm., respectively. A diagnosis of pelvic peritonitis was made and conservative therapy was instituted. Temperature and pulse returned to normal on the fifth day. She was discharged on the twelfth day, at which time the white count was 9,000. Internal pelvic examinations were not done.

Examination in the out-patient department on Oct. 25, 1939, revealed a left tuboovarian mass. At that time, she stated that menometrorrhagia had been present since her discharge from the hospital. A Friedman test was negative. A small cervical erosion was then treated with silver nitrate stick and foreign protein therapy was begun. Menses returned to normal by Jan. 5, 1940. However, a weight loss of fifteen

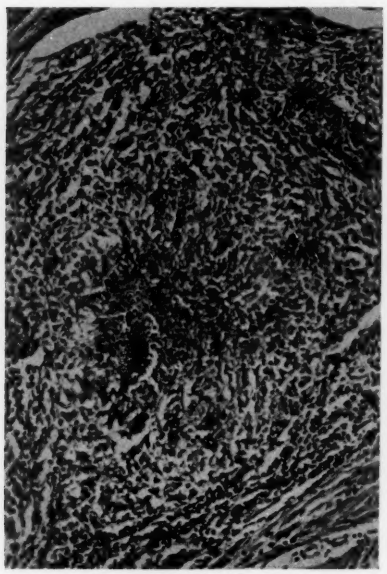

Fig. 2.

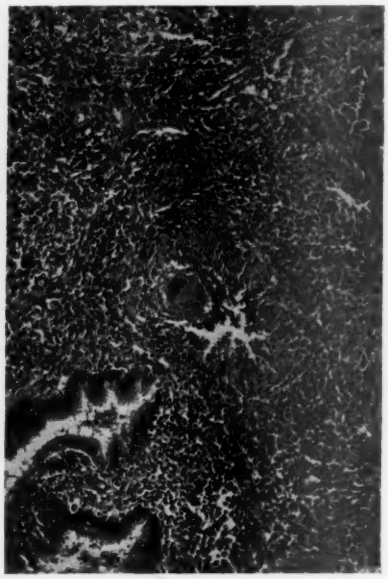

Fig. 3.

Fig. 2.—(S. P. No. 35298.) Tuberculous myometritis. Except for a few smooth muscle fibers at either end, the tissue is not recognizable, being replaced, for the most part, by a tubercle with central necrosis and giant cell formation.

Fig. 3.—(S. P. No. 35298.) Tuberculous endometritis. Endometrial glands are visible at the upper left corner. The rest of the tissue shows inflammation, necrosis, and giant cell formation.

pounds was noted. The cervix, at this visit, was found to be irregular and hypertrophied. There was a friable papillary overgrowth which covered almost half of the anterior lip. The examination caused free bleeding. The cervix was moderately fixed, and the adnexa were not palpable. Hospitalization was advised for biopsy, as a cervical malignancy was suspected and physical examination by the medical department was reported as negative. The patient entered the hospital on Feb. 15, 1940, at which time the only additional findings were an increased weight loss, a slightly larger cervical lesion and moderately increased cervical and parametrial fixation. The rest of the internal examination was unsatisfactory. Curettage of the uterus and biopsy of the cervix were done under nitrous oxide-oxygen anesthesia on the following day. Examination of frozen sections showed tuberculous cervicitis.

During the ensuing two weeks, an attempt was made to rule out other tuberculous foci. No active lesion outside of the pelvis was found. Cystoscopy, retrograde pyelograms, x-ray of the chest, and guinea pig inoculation with sputum and urine failed to disclose active tuberculosis.

Fig. 4.

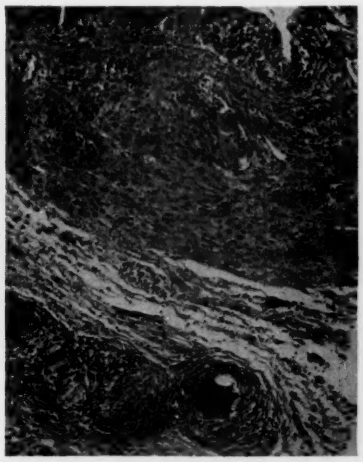

Fig. 5.

Fig. 4.—(S. P. No. 35298.) Tuberculous salpingitis (interstitial). The endosalpinx is visible at the left and shows evidence of a chronic inflammation. The myosalpinx is edematous, and at the right the muscle fibers are separated by an area of degeneration and giant cell formation. In other areas, the endosalpinx was involved, but pictures here could not be distinguished from tuberculous endometritis.

Fig. 5.—(S. P. No. 15861.) Tuberculous oophoritis. The right half shows the wall of a developing follicle. The left contains typical tuberculous inflammation and giant cell formation.

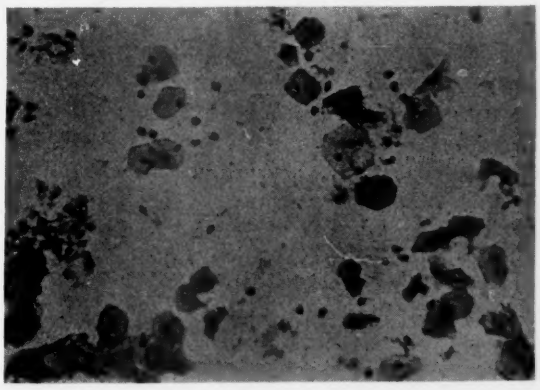

Fig. 6.—Vaginal smear after the method of Papanicolaou showing a moderate estrin deficiency. Both ovaries of this patient were totally removed one year previously. Urinary estrin excretion at this time is over twenty rat units per day.

Despite her age, total hysterectomy and bilateral salpingo-oophorectomy were performed on March 1, 1940, under general anesthesia. The intestines were matted by old firm adhesive bands. No attempt was

made to locate or remove the appendix. The operation was easily performed after separating the adherent bowel from the uterus, tubes, and ovaries.

The pathologic diagnosis was tuberculous cervicitis, endocervicitis, endometritis, myometritis, salpingitis, perisalpingitis, perioophoritis and peritonitis; only the ovaries were uninvolved.

Her convalescence was stormy. She developed intestinal obstruction and was operated upon on March 16, 1940, at which time several bands of firm adhesions in the left upper quadrant were severed; a volvulus was relieved and an enterostomy was done. The patient was discharged on May 8, 1940, after closure of the enterostomy. The midline incision had healed by first intention, and the enterostomy wound was granulating but not draining. She was readmitted on May 12, 1940, with a recurrence of intestinal obstruction following an unwise meal. This was easily relieved by the Miller-Abbott tube and enemas. She was well within ten days but was not discharged until June 4, 1940, at which time she weighed 84 pounds. The combined hospital stay was 106 days. She is now well, weighs 112 pounds, and has returned to normal activity.

There was evidence of surgical menopause after the pelvic laparotomy, but there have been no flushes for the past six months. Vaginal smear after the method of Papanicolaou, done on April 16, 1941, showed only a moderate estrin deficiency. Estrin excretion studies show 20 R.U./24-hour specimen of urine.

There is a slight incisional hernia at the enterostomy site. Reexamination of the surgical specimen disclosed that both ovaries had been totally ablated. The probable source of the estrin now being excreted is either the adrenal glands, or aberrant ovarian tissue.

COMMENT

The question of surgical intervention in this case was not clear at first. Several local internists suggested surgical intervention if no other active lesion was present. Of current literature, only the monographs by Norris[3] and Jameson[2] were of help. Both authors give evidence supporting radical as well as conservative treatment, but prefer the former if active tuberculosis is not present elsewhere. Both state that insufficient data are at hand for a critical evaluation of the various types of therapy. Jameson's work is the most recent, and I quote excerpts which influenced our decision.

On page 68 (et. seq.), he writes: "... failed to find a report of spontaneous healing of tuberculosis of the cervix ... and untreated cases of ulcerative and papillomatous tuberculosis of the cervix tend to progress." "Curettage has been employed with good results, but the method is condemned ... because of the danger of dissemination of the disease." "If tuberculosis of the upper tract is recognized preoperatively, and biopsy of the cervix is positive, one is justified in doing a total hysterectomy." Later he states: "Roentgen-radiation in cervical tuberculosis has failed to give favorable results ... and it is self-evident that radium could have but little effect in the presence of large caseous masses. ..." Of adnexal and uterine tuberculosis (page 131, et seq.) he states: "Experience has shown that cases of tuberculous salpingitis treated by the usual conservative measures employed in common tubal inflammations fail to regress ... but is the only method

justified in certain cases with the possible exception of simple laparotomy or roentgen-ray therapy." In regard to surgery, he comments: "... it is absolutely impossible to determine the extent of the disease macroscopically . . . and bilateral salpingectomy should be done. . . . If . . . removal of the ovaries has been necessitated by extensive adnexal disease, there is no particular value in leaving the uterus in situ. It has been shown . . . that the danger of producing untoward symptoms of premature menopause in young women by oophorectomy is less than in other types of pelvic disease because the internal secretion of the ovary has already been suppressed. . . ."

SUMMARY

The history and pathology of gynecologic tuberculosis have been briefly reviewed. Surgical and autopsy records of 32 patients affected with gynecologic tuberculosis at Mt. Sinai Hospital in Cleveland have been summarized, and the case histories reported. There was no immediate operative mortality. Thirteen patients have not been followed. Four are known to be dead, one with tuberculosis. Six, and possibly 7, are living and apparently free of the disease, while two have active, nongynecologic tuberculosis. The pelvic findings were incidental in 5 of the 6 diagnosed at autopsy. The sixth died one month after delivery. Preoperative diagnosis was seldom correct, and most patients had a septic postoperative course. All drained incisions disrupted, and almost half of the patients left the hospital with draining wounds. Except for a history of menometrorrhagia, dysmenorrhea, and relative sterility, gynecologic history was not typical. A case of an 18-year-old negress with extensive pelvic tuberculosis, who was treated by radical surgery, with apparent recovery, is reported in detail. Various methods of treatment of gynecologic tuberculosis are presented.

I acknowledge the permission to review the case histories summarized above, and express my gratitude to the surgeons who gave that permission. I wish to thank Dr. Kline and his associates in the laboratory for their assistance, particularly Miss Josephine Jones who stained and isolated the tubercle bacilli, and Mr. Wm. Stevenson who photographed the slides.

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FURTHER STUDIES ON THE STERILE AND FERTILE PERIODS IN WOMEN

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CHICAGO, ILL.

THE so-called "safe" period is of special importance for those women who, because of "conscientious objections" or otherwise, would not resort to chemical or mechanical contraceptive measures; and likewise for all those who, on account of esthetic reasons or practical considerations, such as interference with normal sensations or fear of injury to physical or mental well-being, would object to the use of artificial contraceptives.

Because of the pioneer work of two investigators in this field, the safe period principle has been generally known as the "Ogino-Knaus" theory. As explained at length in earlier publications, it proposes the following basic claims under normal conditions:

1. Ovulation occurs fourteen days before menstruation.
2. The life span of the corpus luteum is fourteen days.
3. The ovum is subject to fertilization for only a few hours after its expulsion from the Graafian follicle.
4. The male sperm, within the female genitalia, can fertilize the ovum only within a limited period of time, lasting not more than forty-eight hours.

Although within the last few years many papers have been published containing such statements as, "the safe period is not safe" or, "the safe period is only approximately safe," etc., we have yet to find a controlled report on several hundred women with written records of their menstruations and coitus which serve to prove the validity of the claims of "Rhythm" babies. Memory records, as so often pointed out, are notoriously faulty, and unfortunately many women receive the wrong information based upon the old Capellman theory or upon an erroneous conception of the method under discussion.

Many couples making use of the "safe period" during the past few years have kept accurate written records of the dates of the beginning of their menstruations, of the actual dates of cohabitations, and of the various extrinsic factors which might have led to disturbances in ovulation and the normal functioning of the corpus luteum. We were gratified by the intelligent cooperation of most of our patients. The analysis of their reports, received from July, 1937, to June, 1940, form the basis of the present communication. Most of this material is graphically outlined in three charts.

Chart 1 depicts the records of 24 women who at first used the sterile periods to avoid pregnancy and later cohabitated in the fertile periods and conceived.

The figures in the first horizontal line of each case indicate the number of cohabitations that took place on the listed days of the cycle, none of which resulted in a pregnancy. The figures in the column under the heading "months" indicate the number of months the method was used according to available records. The figures headed "total" refer to the number of cohabitations which occurred during the sterile periods while conception was to be avoided.

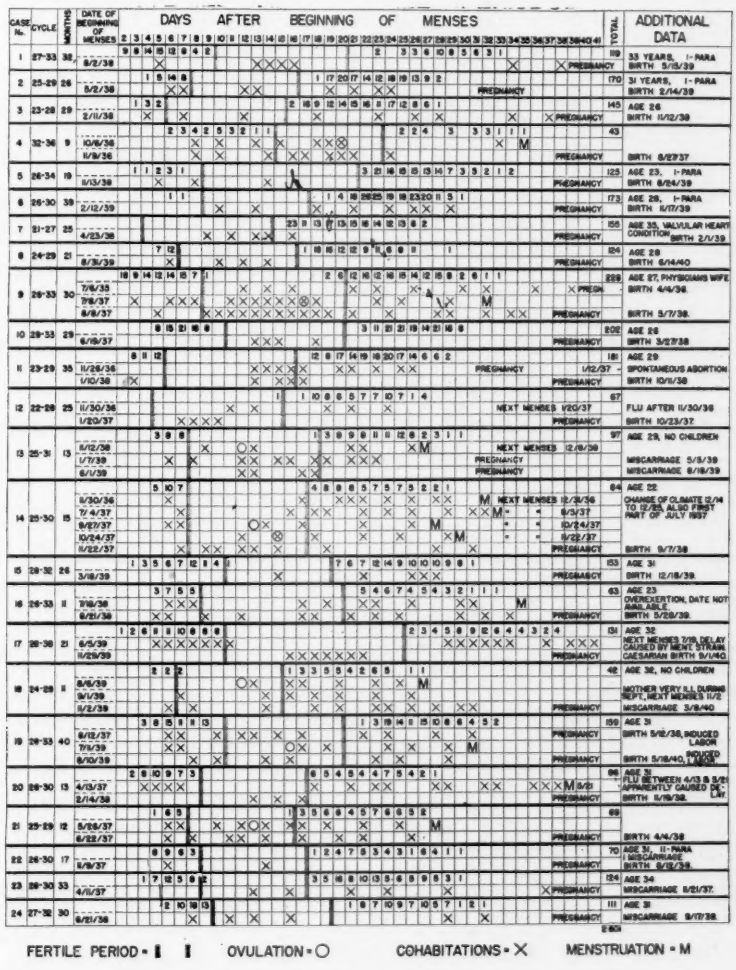


Chart 1.

Cases 1, 2, 3, 5, etc., are self-explanatory. Cases 4, 9, and 21 need classification. There could have been a pregnancy one menstrual month before conception took place. Why pregnancy did not occur at that time is conjectural. Coitus was well timed within the fertile period, but did not result in pregnancy.

Cases 12, 14, 16, 17, 18, and 20 serve to illustrate the effect of certain temporary disturbances. During the menstrual cycle of Case 12, which began Nov. 30, 1936, there was a "flu" episode and the following

menses did not occur until Jan. 20, 1937. This resulted in an extraordinary fifty-one-day cycle and is probably attributable to the influenza. In the menstrual month beginning Jan. 20, 1937, there were four cohabitations within the fertile period, namely on the seventh, eighth, ninth, and tenth days of the cycle, during which time this woman conceived; the baby was delivered on Oct. 23, 1937.

Case 14 presents unusual features. In the menstrual month beginning Nov. 30, 1936, coitus took place on Dec. 16, which was the fifteenth day before the onset of the next menses (December 31), yet conception failed to occur. The change of climate, experienced between December 14 and 25, might conceivably have prolonged the life span of the corpus luteum to more than the conventionally accepted fourteen days, if we assume that ovulation occurred before December 16. The climate change during the first part of July, 1937, might explain why no conception occurred on the sixteenth, eighteenth, and nineteenth days of the cycle (July 19, 21, and 22), during the menstrual month beginning July 4. Ovulation probably occurred before July 19. In the menstrual month commencing Sept. 27, 1937, there was no conception because intercourse took place on the day following ovulation; likewise, in the menstrual month commencing Oct. 24, 1937, the woman had intercourse on the assumed ovulation day, yet menstruation occurred November 22. In the subsequent menstrual month there was evidently a fertile intercourse and a child was born on Sept. 7, 1938.

Cases 16, 17, 18, and 20 may be interpreted in a similar manner.

In summary, Chart 1 indicates that cohabitations executed during the sterile periods do not cause pregnancy, whereas intercourse properly timed and executed during the fertile period eventually results in conception if male and female are fertile.

When we review the ten cases, 25 to 34, appearing on Chart 2-A, we find that with the exception of Case 30, all these women had borne one or more children at one time or another, and we may assume therefore that nine of these women are probably fertile. Because of some disturbing extraneous influence, there was a delay in menstruation in Cases 25 to 31 and in Case 33. When we notice, especially in Cases 26, 28, 30, and 31, the time of the intercourses preceding these delayed menstruations, we wonder why pregnancy did not result since copulation took place on or about the fifteenth day before the onset of menstruation. We might enter the realm of conjecture and postulate anovulatory menstruation, temporary sterility, or a prolongation of the life span of the corpus luteum, due to the upsetting factors, as mentioned under "additional data." The latter assumption probably approximates the actual facts.

By the same process of reasoning, one might assume that physical or mental strain, as well as other disturbing factors, such as physical or mental shock, unusual exertion, change of climate or altitude, certain medication, etc., could shorten the accepted viability of the corpus luteum as demonstrated in Cases 32 and 34.

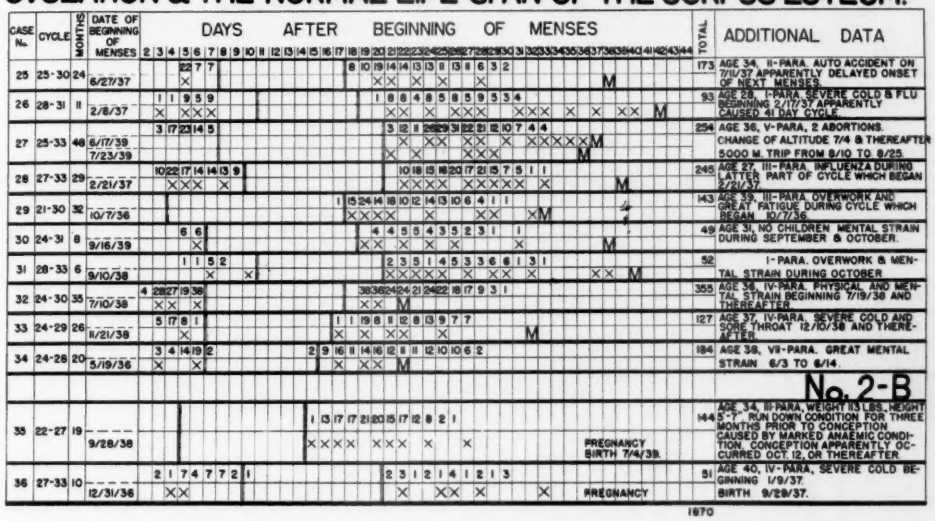
If the women representing Cases 25, 26, 27, 30, and 32 intended to avoid conception, and to all appearances this seems to have been their intention, then these cases illustrate the typical faulty application of the method. There was no assurance that ovulation had taken place when the extraordinary event, which apparently resulted in a disturbance, had occurred or began to occur. The particular extraordinary event might have delayed ovulation and abstinence should have been practiced until

the disturbance had passed and until the menstrual cycle which might have been affected had terminated. For instance, in Case 25 an automobile accident occurred on July 11, which was the fifteenth day of the cycle and as ovulation might have been considerably delayed, this woman should have abstained until the beginning of the next menses. This is particularly true if she did not want to take any chances of becoming pregnant.

In summary, Cases 25 to 34 seem to show that temporary disturbances of various character delay or hasten the function of the corpus luteum as well as the onset of the next menstruation.

No. 2-A

EXTERNAL INFLUENCES WHICH APPARENTLY DISTURB OVULATION & THE NORMAL LIFE-SPAN OF THE CORPUS LUTEUM.


CASE No.
CYCLE
MONTHS
DATE OF BEGINNING OF MENSES
DAYS AFTER BEGINNING OF MENSES
TOTAL
ADDITIONAL DATA
25 25-30 24 6/27/37 173 AGE 34, II-PARA. AUTO ACCIDENT ON 7/11/37 APPARENTLY DELAYED ONSET OF NEXT MENSES.
26 28-31 II 2/8/37 93 AGE 28, I-PARA. SEVERE COLD & FLU BEGINNING 2/17/37 APPARENTLY CAUSED 41 DAY CYCLE.
27 25-33 48 6/17/39 7/23/39 254 AGE 36, V-PARA, 2 ABORTIONS. CHANGE OF ALTITUDE 7/4 & THEREAFTER 5000 M. TRIP FROM 6/10 TO 6/25.
28 27-33 29 2/21/37 245 AGE 27, III-PARA. INFLUENZA DURING LATTER PART OF CYCLE WHICH BEGAN 2/21/37.
29 21-30 32 10/7/36 143 AGE 39, III-PARA. OVERWORK AND GREAT FATIGUE DURING CYCLE WHICH BEGAN 10/7/36
30 24-31 8 9/16/39 49 AGE 31, NO CHILDREN. MENTAL STRAIN DURING SEPTEMBER & OCTOBER.
31 28-33 6 9/10/36 52 I-PARA. OVERWORK & MENTAL STRAIN DURING OCTOBER
32 24-30 35 7/10/38 355 AGE 36, IV-PARA. PHYSICAL AND MENTAL STRAIN BEGINNING 7/19/38 AND THEREAFTER.
33 24-29 26 11/21/38 127 AGE 37, IV-PARA. SEVERE COLD AND SORE THROAT 12/10/38 AND THEREAFTER.
34 24-28 20 5/19/36 184 AGE 38, VII-PARA. GREAT MENTAL STRAIN 6/3 TO 6/14.
No. 2-B
35 22-27 19 9/28/38 144 AGE 34, III-PARA, WEIGHT 113 LBS., HEIGHT 5'-7". RUN DOWN CONDITION FOR THREE MONTHS PRIOR TO CONCEPTION CAUSED BY MARKED ANAEMIC CONDITION. CONCEPTION APPARENTLY OCCURRED OCT. 12, OR THEREAFTER
PREGNANCY BIRTH 7/4/39.
36 27-33 10 12/31/36 91 AGE 40, IV-PARA. SEVERE COLD BEGINNING 1/9/37.
PREGNANCY BIRTH 9/29/37.
1870

FERTILE PERIOD = | | COHABITATIONS = X MENSTRUATION = M

Chart 2.

Chart 2-B illustrates the only two involuntary pregnancy cases in our files of which satisfactory written records are available; however, even these records are not entirely complete. It should be stated that besides these two cases, we were informed of 26 additional undesired pregnancies. From the information which we could extract, it is apparent that the great majority of these 26 additional cases were caused by faulty application of the method, the use of contraceptives or the practice of retractions during the fertile period.

The woman represented in Case 35 became pregnant while cohabitating outside of the fertile period, as established by a record kept for eighteen months prior to February, 1937, when she was seeking advice regarding natural conception control. As she was underweight and as a secondary anemia was suspected, she was instructed to consult her family physician for her blood condition and, if necessary, have a blood count made. This examination was made and found negative; however, it was revealed that an anemia existed in 1933.

Although the patient was warned against practicing natural conception control during the recurrence of the secondary anemia and al-

though her record calendar indicates a continuous run-down condition beginning with July, 1938, she continued to use the method as shown. She apparently conceived on Oct. 12, 1938, or shortly thereafter. A child was born on July 4, 1939. The duration of the pregnancy was about 265 days. The family physician had prescribed an iron tonic when he was consulted because menstruation failed to occur during the latter part of October, 1938. Apparently no other disturbances took place and therefore anemia seems to be a contributing factor to this failure. There is no record of a blood count made in October, 1938, and our information is necessarily, therefore, inadequate. Since a marked anemic condition usually delays a woman's cycle, we are inclined to believe that secondary anemia was the cause of this pregnancy.

TABLE SHOWING NUMBER OF STERILE COHABITATIONS EXECUTED DURING LISTED DAYS OF CYCLES. No. 3

| NUMBER OF WOMEN | NUMBER OF CYCLES | CYCLE | DAYS AFTER BEGINNING OF MENSTRUATION | | |

the number of times these cycles occurred. Correspondingly, in Column 1, we listed the number of women who had experienced these cycles. For example, 342 women recorded a thirty-day cycle 784 times; these same women, of course, had other cycles listed elsewhere. In the body of the chart are recorded the number of intercourses had on the various days of the cycle. Ovulation is shown by a black dot. For example, the 223 women who had a twenty-four-day cycle 724 times, had ten cohabitations on the second, 32 cohabitations on the third, 78 cohabitations on the fourth, etc., days after the onset of menstruation. All told, there are 11,249 cycles listed, with 49,356 intercourses, and conception failed to occur.

Chart 3 furnishes the practical proof that ovulation must occur about as shown, that the time for fertilization of the ovum is very short, and that the life of the sperm cells inside the female genitals is limited to less than forty-eight hours. If this were not the case, a number of pregnancies should have occurred, as it cannot be assumed that a higher than average percentage of the couples who furnished the data for this chart are sterile.

In addition to the 4,702 cohabitations executed by 114 couples and reported in the *Journal of the American Medical Association*, Oct. 19, 1935, and the 11,222 cohabitations of 265 couples published in the *Illinois Medical Journal*, March, 1937, we have reported in this paper, 54,027 cohabitations which were executed during the sterile periods, listed in Charts 1 to 3, giving further evidence that abstinence during the fertile period prevents conception.

CONCLUSIONS

This factual evidence confirms our belief that the biologic law of sterility and fertility as originally propounded by Knaus is correct, essentially practical and workable.

209 South State Street

Escomel, Elmundo: Therapy of Enteritis, Vaginitis, Cystitis and Gingivitis Produced by Trichomonad Infestations, Presse méd. **48**: 172, 1940.

The writer, a Peruvian physician, states that trichomonad cases are observed rarely in Europe. He observes that this type of protozoan infestations is frequent in colonial French Africa, Asia, and in the three Americas. In the subtropical and tropical Americas the incidence of trichomonad infestation is regarded as even greater. These statements are not supported by statistical data.

For vaginal trichomonorrhea the author recommends two daily douches with 1:1,000 solution of oxycyanide or a 1:4,000 solution of potassium permanganate. Each irrigation is followed by drying the vaginal canal and leaving a tampon, soaked in Franck's emulsion, a mixture of turpentine, laudanum and gum syrup. The medicated tampon is used twice daily for a period of three days. The vulva and vestibule are protected by vaseline and a vulvar pad.

Relief from vesical trichomoniasis is obtained by daily instillations of this emulsion into the bladder, without previous lavage. This is done for three days.

Clair E. Folsome.

A CLINICAL AND PATHOLOGIC STUDY OF 115 CASES OF TUBAL PREGNANCY

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THIS communication is a study of 115 patients with tubal pregnancy operated upon at the City Hospital, Welfare Island, New York City, from 1922 through 1939. The clinical conclusions correspond in the main to generally accepted concepts, though in two respects they differ from prevailing views. First, the duration of amenorrhea seemed to depend more on the type of implantation than upon its site. The erythrocyte sedimentation rate was not found entirely reliable in differentiating pelvic inflammatory disease from ectopic pregnancy. The histologic examinations led to conclusions very different from the more accepted views. The cause of ectopic pregnancy could not be determined from the condition of the tube in a great number. Decidual reaction was very common and appeared to be a response to the chorionic villi present and to their state of preservation.

Since the clinical data were obtained from the hospital records, the composite work of attending and resident staffs over a long period, the observations and interpretations showed variations due to the changing concepts year after year. Conclusions in this study were made bearing this factor in mind.

The ages ranged from 19 to 38 years, the average being 29. Sixty-eight, or 59 per cent, were between 25 and 34 years. These data correspond closely to those of Schumann.[1] He reported 60 to 70 per cent of ectopic pregnancies occurring between 24 and 33 years. Fitzgerald and Brewer[2] reported a case in a woman 49 years old. In Darley's[3] case, the patient was only 12. We did not find these extremes in our series.

Ectopic pregnancy occurred in 71 white and in 39 colored women, a percentage of 64.5 and 35.5, respectively. It is impossible to state whether this represents a true proportion since the ratio of colored to white patients admitted to the service for the period studied is not available. However, Langman and Goldblatt[4] reported that at Bellevue Hospital, where 40 per cent of the gynecologic patients were colored, only 11 per cent of the total ectopic pregnancies were found in this group. These data strongly suggest that the white race is the more prone to develop this condition.

There had been previous pregnancies in a high percentage of the cases. Eighty-five patients, or 77 per cent, had normal uterine pregnancies preceding the tubal gestation. The number of pregnancies ranged from 1 to 8 and the average was 2.8. It was noteworthy, however, that 48.3 per cent of the multiparas had a period of sterility of three years or more between the last uterine pregnancy and the ectopic gestation. Thus despite a high degree of fertility in the women who developed ectopic pregnancy, a sterile period preceded the abnormal pregnancy in about half the cases.

The one constant symptom was pain, which was presented in all of the 115 cases. Grier,[5] Fitzgerald and Brewer, and Ricci and Di Palma[6] also emphasized the importance of pain as a constant finding. The character of the pain varied according to the pathologic process. In the cases of ruptured tube, the pain was frequently sharp, at times cramplike, but almost never dull. It was usually generalized or in the lower abdomen, severe, more often continuous than intermittent, referring occasionally to the shoulder and less often to the rectum. The tubal abortions were accompanied by pain resembling that seen in uterine abortions, cramplike rather than sharp, intermittent, severe and lower abdominal. The unruptured tubal gestations had sharp intermittent pain. Falk[7] states that pain is due to distention of the tube by hemorrhage and is not the result of pressure from a growing ovum.

Menstrual disturbance was the next most common symptom, occurring in 113 of the 115 cases. The disturbance was usually a period of amenorrhea followed by vaginal bleeding. Vaginal bleeding was present in 97 and amenorrhea in 92 cases, either singly or together. The bleeding was described as "profuse," "spotting" or "mixed with clots." No one type was constant either in rupture or in abortion. It was noted, however, that in unruptured gestations the bleeding was often described as "scant and dark brown." It is unlikely that a true history of missed period or abnormal bleeding was always obtained, because patients will frequently call the "spotting" a normal period if it occurs at the time a period is expected.

There was no demonstrable relation between the duration of amenorrhea and the site of nidation in pregnancies which terminated by rupture. The duration was 51.6 days in the interstitial, 53.7 in the isthmic, and 51.5 in the ampullary pregnancies. These findings were contrary to the generally accepted belief that cases of isthmic gestation rupture earlier than the interstitial or ampullary types.

A significant difference was found in the length of amenorrhea in the abortions, and it is the belief of the authors that this difference depends mainly upon the type of nidation. In the abortions the duration was 40.5 days, in ruptures 52.2 days, and in unruptured pregnancies 53 days. It is generally accepted that the type of nidation, whether luminal or mural, determines the pathology which follows. In luminal

implantation, the pseudocapsularis is notoriously weak and prone to early rupture. This fact probably is the underlying factor in the shorter duration of amenorrhea in abortion.

The less common symptoms were recorded only when present. Vomiting was noted in 30 cases, fainting in 25, nausea and weakness each in 19 and dysuria in 8. Indications of pregnancy aside from amenorrhea were decidedly infrequent. Only 4 patients had morning sickness and 3 had swollen breasts.

The most common sign obtained by abdominal examination was tenderness, which was found in 88 cases. Other findings were less frequent. Rigidity was present in 32 cases, rebound tenderness in 29 and distention in 12. It is likely that distention occurred more frequently than indicated in this series, and that Falk was correct when he stated that "abdominal distention is a very frequent sign that is overlooked."

Palpable masses on pelvic examination were as frequent as abdominal tenderness. They were adnexal in 64 cases, cul-de-sac in 13, and combined cul-de-sac and adnexal in 11 cases. When masses were found in the cul-de-sac, the clinical evidence pointed to repeated small hemorrhages. These probably led to periodic increases in blood clot organization and tumor formation. With a single massive hemorrhage, surgical procedures were carried out too early to permit masses to form. The isthmic gestations particularly seemed prone to be associated with single large hemorrhages.

Cervical changes were found less frequently than pelvic masses. The cervix was tender on motion in 39, soft in 30 and blue in 6 cases. Quite frequently more than one change was seen in the same cervix.

Diagnostic colpotomy was performed in 9 cases. Free blood was found in 8 while all cases were ruptured. The value of this procedure seems doubtful. A negative result does not disprove the presence of ectopic pregnancy. Furthermore, Grier reported a long stormy convalescence following its use.

Diagnostic curettage was performed in 9 cases. A decidual reaction of the endometrium was found in 5, a proliferative endometrium in 3 and a menstrual endometrium in 1. In the last four, rupture had occurred some time previously. The report "decidual reaction, no chorionic villi seen," while suggestive of ectopic pregnancy, is not pathognomonic. A decidual reaction alone may be found in a high percentage of curettages in cases of incomplete abortions. Nor does the absence of a decidual reaction eliminate the diagnosis of ectopic pregnancy. In an ectopic pregnancy which has ruptured a few weeks before the patient is admitted, the uterine decidua may have been cast off and replaced by a proliferative endometrium. The curettage is of definite value only when chorionic villi are found, which show that the case is definitely one of intrauterine pregnancy.

Leucocyte counts, done in 83 cases, showed a range of 5,800 to 28,000. In the abortions and ruptures, the average counts were approximately the same, 11,950 and 12,720, respectively. A few patients with rupture had normal counts, when the rupture had occurred a month or more previously. The unruptured gestations had counts on the average only slightly lower, 10,480. The differential blood picture was of more significance than the total counts. In rupture, the average neutrophilic percentage was 80.5; in abortion 67.7. The unruptured cases were too few to permit the drawing of any conclusions. Changes in the leucocyte counts appeared to be more closely related to the presence of initial intraperitoneal hemorrhage than to the pregnancy. Ricci (1931) also suggested this interpretation. He found an initial leucocytosis occurring at the time of intra-abdominal spill, followed by a gradual decline. In the present series repeated counts were not done. However, it seems evident that the gradual fall in a ruptured ectopic pregnancy differs from the persistent leucocytosis of inflammatory disease.

Erythrocyte counts and hemoglobin determinations were done in 93 cases. The red blood cell counts ranged from 800,000 to 5.5 million; the hemoglobin percentages from 20 to 100 per cent. In abortions, the average red cell count was 3.67 million and the average hemoglobin 62.7 per cent. In rupture they were 3.1 million and 58.5 per cent. These determinations proved of value as an indication of blood loss.

The erythrocytic sedimentation rate was estimated in 80 cases by the Linzenmeir method. Sixteen cases, or 20 per cent, had a rate of thirty minutes or less. Urdan[8] had identical findings in 44 cases. In a group of 30 cases, Tenney[9] found 10 per cent with a rapid rate. The increased sedimentation rate appeared to be due to the pregnancy itself in the majority of instances. Acute salpingitis was found in only two cases. In the other 14, neither the pathologic data nor the clinical findings revealed any inflammatory disease which could have been responsible. The degree of anemia did not offer an adequate explanation. The average red cell count was 3.1 million and the average hemoglobin 56.7 per cent. In 64 cases with sedimentation rates above thirty minutes, the corresponding figures were 3.2 million and 64 per cent.

Friedman tests were carried out in 11 cases. Eight were positive and 3 were negative. In the latter, clinical evidence indicated that rupture had probably occurred a month or more previously. Furthermore, the histologic examinations revealed markedly degenerated chorionic villi, apparently incapable of secreting the anterior pituitary-like substance responsible for a positive result.

The site of pregnancy as determined at the operating table was tubal in 93 per cent, secondary abdominal in 3 per cent, ovarian in 2 per cent, and unidentified in 2 per cent. The ovarian pregnancies proved on further laboratory examination to be secondary implants and not primary ovarian gestations. Of the 115 cases, 65.3 per cent were ampullary,

23.4 per cent isthmic, and 6.3 per cent interstitial. In this series, the incidence of interstitial implantation was higher than most observers have reported. Solomons[10] found 2.3 per cent among 183 cases. Among 3,982 cases collected from the literature by Wynne,[11] there were 1.5 per cent. In the 278 cases of Puetz[12] there were 2.4 per cent. Rupture occurred in 79.6 per cent, abortion in 14.9 per cent, and 5.5 per cent were unruptured.

There was practically the same incidence of ectopic pregnancy on each side. The right was involved in 59; the left in 52. Lavell[13] and Urdan found that previous surgery had a tendency to localize the pregnancy to the side on which the surgery had been done. In the present series, this did not hold true. Previous lower abdominal operations had been performed in 17 cases, among which were 12 appendectomies. Left- and right-sided gestations were equally distributed among the latter.

Histologic sections of 101 cases were available for restudy. Serial sections were not done. Six cases had slides only through the site of implantation. In the remaining 95, other portions of the tubes had been sectioned. Fifty-eight tubes were perfectly normal except for the local changes at the site of implantation. There was evidence of salpingitis in 37, of which 25 cases were classified as intense and 12 as mild. Chorionic villi were present in 83. They were well preserved in 32, slightly degenerated in 9, and greatly degenerated in 42. Decidual reaction was found in 43. It was always patchy and abortive and never very extensive. In 36 of the 43 cases where a decidual reaction was found, the chorionic villi were fresh or only slightly degenerated. These observations suggest that the presence of decidual tissue may depend upon hormones secreted by the chorionic villi, and that at the point of implantation a decidualike reaction probably occurs in a high majority of cases.

The type of imbedding could be determined in only 15 instances. It was mural in 9, luminal in 5, and combined luminomural in 1. At no time was endometrial tissue seen at the site of nidation. An intact fetus was found in 8 cases. Embryonic parts were present in a blood clot in one instance.

Investigations centered on the Fallopian tube in an attempt to find an explanation for the occurrence of ectopic pregnancy have not led to universally accepted conclusions. Falk believes that preceding tubal disease is the deciding factor. In his series, he found evidence of previous or existing disease in 90 per cent of the cases and holds that this high incidence proves a causal relationship. In the present series and in other series reported in the literature, such a high incidence has not been encountered. Tubal disease, however, may account for a certain number. Frankel advanced the theory that nidation occurs in a focus of ectopic endometrium and that the amount of this ectopic tissue

capable of undergoing decidual reaction determines the fate of the gestation. The present authors agree that decidual reaction is almost constantly present. However, none of the cases of the present series definitely showed an endometriosis of the tube, and in fact very rarely have the authors seen it in nonpregnant tubes removed for other causes.

Perhaps a more fertile field for investigation would lie in the study of the ovum itself. It has been pointed out by many observers that the fetus of an ectopic pregnancy frequently shows abnormalities. No findings in this series bear out this theory.

The admission diagnosis was correct in 54.3 per cent and incorrect in 45.7 per cent. In the latter, the patients were admitted for salpingitis (29 cases), uterine abortion (11 cases), appendicitis (5 cases), and ovarian cyst (5 cases). However, a correct preoperative diagnosis was made in the great majority of cases after a suitable period of observation. In only a small number was a correct diagnosis made only at operation.

A postoperative morbid course occurred in 14 cases. The complications were pneumonia 3, pulmonary infarction 2, pyelonephritis 2, peritonitis 2, abdominal wall abscess 1, fecal fistula 1, evisceration 1, and severe shock 1. Five patient died, a mortality rate of 4.3 per cent. The causes of death were secondary abdominal hemorrhage, postoperative shock, peritonitis, pneumonia, and cerebral embolism. The mortality rate of this series corresponds closely to those reported by others. In a survey of 3,314 cases collected from the literature by Woodhouse,[14] the mortality rate was 4.46 per cent, almost identical to that of this series. It is of interest to note that during the last six years, although many more cases were observed than in any previous six-year period, there were no fatalities. Two factors appeared responsible: the establishment of a blood bank and the use of cyclopropane anesthesia.

SUMMARY AND CONCLUSIONS

A study of 115 cases of tubal pregnancy is reported. In the main, clinical conclusions agree with generally accepted concepts. The condition occurred more frequently among white women than among colored. About 75 per cent of the patients had previous normal intrauterine pregnancies. A sterile period of three years or more occurred in about half the multiparas prior to the ectopic pregnancy. Symptoms of pain and some menstrual disturbance, usually amenorrhea followed by vaginal bleeding, were present in almost every case. The character of the pain varied with the pathologic process. The duration of amenorrhea appeared to bear no relation to the site of nidation but instead appeared to be related to the type of imbedding. Abdominal and pelvic examinations gave valuable data. Diagnostic colpotomy and curettage were of doubtful value. The erythrocytic sedimentation rate was not

entirely reliable in differentiating pelvic inflammatory disease from ectopic pregnancy. Interstitial pregnancies were found in a relatively large percentage. Previous lower abdominal operative procedures were not found to influence the location of the pregnancy. A decidual reaction of the endosalpinx was present in a large number. The theories advanced thus far to explain the occurrence of tubal pregnancy seem inadequate. It is suggested that the study of the ovum may be a field worthy of investigation.

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THE INHIBITION OF LACTATION DURING THE PUERPERIUM BY METHYL TESTOSTERONE

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A CONSIDERABLE number of reports have been made concerning the post-partum inhibition of lactation by the administration of hormones and similar substances.

In view of the excellent reports on the intramuscular use of testosterone propionate,[1-5] the following study was undertaken to determine the effectiveness of the orally active methyl testosterone.*

As has already been pointed out,[1] the inhibition of lactation in the post-partum woman is almost always a painful process. Testosterone injections have afforded a safe and effective method of greatly alleviating the soreness, congestion, secretion, and malaise that so often accompany the process of "drying-out." The convenience of such a method is obvious to patient and physician.

*We are indebted to Dr. L. Pirk and the Roche Organon Co., for their generous supply of methyl testosterone tablets (Neo-Hombreol (M) Tablets).

During the period of gestation the breasts have been prepared for lactation by the large amounts of estrogenic and corpus luteum hormones in the circulating blood stream. Actual lactation, however, seems to be initiated by the pituitary lactogenic factor (prolactin, Riddle).

Immediately after delivery the concentration in the blood of these ovarian and placental hormones drops abruptly and apparently releases the inhibition on the above lactogenic factor. Within forty-eight to seventy-two hours the breasts fill up with colostrum and then with true milk.

If, however, the lactogenic factor can be inhibited during the early puerperium, the actual flow of milk can be cut off at the fount. The normal breast congestion and secretion can, therefore, be either completely eliminated or reduced to a transient minimum. Increased comfort for the patient, reduced possibility of breast complications and less nursing care will be the result.

METHODS AND RESULTS

Twenty-five cases were selected for the test. They included ward and private cases from the Sloane Hospital and Vanderbilt Clinic and in each case it had been decided, for medical or psychologic reasons, that lactation be terminated. Wherever possible, a multipara was chosen so that the patient might offer her comparison between the present methyl testosterone therapy and any formerly used method of drying up of her breasts. For the most part these women all gave histories of difficulties with lactation in their earlier puerperia. Such difficulties varied from simple congestion to lactorrhea, mastitis, and breast abscesses.

When given intramuscularly, it was found that 100 mg. of testosterone propionate given in 4 divided doses of 25 mg. each, over a period of forty-eight hours was usually sufficient to inhibit lactation and to afford relief to the patient.

The patients included in this study received from 100 to 350 mg. of methyl testosterone in divided doses. In most cases the administration was started between thirty and forty-eight hours after delivery.

Except for a loosely applied breast support no additional therapy was given. Tight breastbinders were abolished and there was no restriction of fluids, milk, cream, or butter. No purging with epsom salts was ordered and neither ice caps nor sedatives were required.

The effectiveness of the treatment was judged by the amount of breast congestion, secretion, and discomfort. The results are summarized in Table I.

Those cases in which there was complete inhibition of colostrum and milk and neither congestion nor discomfort were rated as "excellent." Those where secretion of colostrum, but no milk, was observed, with transient congestion and discomfort not lasting more than twelve hours, were called "very good." Cases where secretion, congestion and tenderness were moderate and persistent for more than thirty-six hours after cessation of medication were rated as "fair," and those where secretion, congestion and discomfort were marked and persistent for more than forty-eight hours after the administration of the last dosage were deemed "poor."

TABLE I. SUMMARY OF RESULTS

CASE	PREVIOUS LACTATION HISTORY	TIME OF TREATMENT AFTER DELIVERY	METHOD OF TREATMENT ON FIRST DAY	SECOND DAY OF TREATMENT	TOTAL DOSAGE	CHARACTER OF PUERPERIUM	RESULT
1	Mastitis and breast abscess with previous pregnancy	4 days	50 mg. q. 3 h. for 4 doses	30 mg. q. 4 h. for 3 doses	290 mg.	Mild congestion, tenderness. Scant secretion during course of medication. Complete relief 48 hours after last administration of methyl testosterone	Good
2	Multiple breast abscesses with previous pregnancy	24 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion, tenderness. Scant secretion during course of medication. Complete relief 24 hours after last administration of methyl testosterone	Good
3	Mastitis and breast abscess	30 hours	40 mg. q. 3 h. for 4 doses	30 mg. q. 3 h. for 3 doses	250 mg.	No secretion, pain, or congestion at any time	Excellent
4	Bilateral mastitis and lactorrhea for one year	12 days	40 mg. q. 3 h. for 4 doses	35 mg. q. 3 h. for 3 doses	300 mg.	Secretion, congestion, and pain reduced by 50 per cent by end of first day of treatment; 75 per cent less by end of second day. Complete relief 24 hours after last dosage	Excellent
5	Primipara	72 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Congestion, secretion, and pain moderate at onset of treatment. Reduced by 75 per cent 24 hours after last dosage. Complete relief 48 hours after last dosage	Good
6	Moderate congestion and pain with previous pregnancy	35 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during two days of treatment but no secretion. Complete relief 48 hours after last dosage	Good
7	Primipara	36 hours	40 mg. q. 4 h. for 5 doses	None	200 mg.	Mild congestion and secretion during treatment. Complete relief 24 hours after last dosage	Good

8	Moderate congestion and pain with previous pregnancy	34 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate secretion, congestion, and discomfort persisting for 3 days after last dosage	Fair
9	Moderate congestion and pain with previous pregnancy	8 days	50 mg. q. 3 h. for 4 doses	None	200 mg.	Marked secretion, pain and congestion from third to eighth post-partum day. Complete relief 36 hours after last dosage	Excellent
10	Primipara	36 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	Slight congestion during dosage. Never any secretion or pain	Excellent
11	Moderate congestion and pain with previous pregnancy	35 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	No secretion, pain or congestion at any time	Excellent
12	Primipara	72 hours	50 mg. b.i.d.	None	100 mg.	Moderately severe congestion, secretion, and pain persisting for one week after treatment	Poor
13	Mastitis after previous delivery	36 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	Slight congestion during dosage. Never any pain or secretion	Excellent
14	Moderate congestion and pain after previous delivery	5 days	50 mg. q. 4 h. for 3 doses	None	150 mg.	Full secretion with congestion and tenderness at start of dosage; 75 per cent relief 48 hours after last dosage. Complete relief in 72 hours	Good
15	Moderate congestion and pain after previous delivery	36 hours	50 mg. q. 4 h. for 3 doses	30 mg. q. 4 h. for 3 doses	240 mg.	Mild congestion during treatment. Never any secretion. Complete relief 36 hours after last dosage	Excellent
16	Severe congestion and pain after previous delivery	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during treatment. Never any secretion. Complete relief 24 hours after last dosage	Excellent
17	Primipara	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during treatment. Sudden congestion and scant secretion on 6th day after treatment, lasting only 8 hours	Good

TABLE I—CONT'D

CASE	PREVIOUS LACTATION HISTORY	TIME OF TREATMENT AFTER DELIVERY	METHOD OF TREATMENT ON FIRST DAY	SECOND DAY OF TREATMENT	TOTAL DOSAGE	CHARACTER OF PUERPERIUM	RESULT
18	Mastitis after previous delivery	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate congestion. Secretion and pain for 3 days after treatment	Fair
19	Primipara	42 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Never any secretion, congestion, or pain	Excellent
20	Profuse secretion of colostrum starting during third month of pregnancy	33 hours	50 mg. q. 4 h. for 4 doses	50 mg. q. 4 h. for 3 doses	350 mg.	Lactation profuse at onset of medication and remained profuse up to eighth day post partum when 50 mg. of methyl testosterone was given t.i.d. Flow after that diminished. Never any pain, but secretion persisted for 16 days post partum	Poor
21	Marked congestion and pain after previous delivery	38 hours	50 mg. q. 3 h. for 2 doses	30 mg. q. 3 h. for 5 doses	250 mg.	Scant congestion and secretion during treatment. Never any pain. Complete relief 36 hours after last dosage	Good
22	Marked congestion and pain after previous delivery	32 hours	50 mg. q. 3 h. for 2 doses	30 mg. q. 3 h. for 3 doses	190 mg.	Scant congestion during first day of treatment. Never any secretion or pain	Excellent
23	Marked congestion and pain after previous delivery	39 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Scant secretion, and congestion for 24 hours after last dosage. Never any pain	Good
24	Primipara	30 hours	50 mg. q. 4 h. for 4 doses	50 mg. b.i.d.	300 mg.	Moderate secretion, congestion, and discomfort for 36 hours after last dosage	Good
25	Moderate congestion and pain after previous delivery	26 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate secretion, congestion, and discomfort for 48 hours after last dosage	Fair

Of the 25 patients treated with methyl testosterone, 10 were graded

TABLE II. RESULTS

RATING	NO. OF CASES
Excellent	10
Very good	10
Fair	3
Poor	2

as "excellent," since in these there was no secretion at all, and neither congestion nor tenderness of the breasts at any time.

Ten cases were graded "very good" since there was mild congestion, tenderness, and secretion of colostrum only, for twelve to twenty-four hours after the administration of the drug. Three cases were called "fair" since there was moderate secretion of milk with congestion and tenderness of the breasts during the course of medication or lasting as long as two days after administration of the last dosage. Two cases were called "poor" but in the first of these (Case 12), the medication was not started until seventy-two hours after delivery and at that time the breasts were already engorged, painful, and actively secreting. Here, too, the complete dosage was not given as the result of an oversight and the patient's breasts remained painful, engorged, and actively secreting for one week. The other case (Case 20) rated as "poor" was an unusual one. She was a 22-year-old gravida ii, para ii, whose baby died a few hours after birth. Her ante-partum course was one of severe toxemia and hypertension. With her first pregnancy in 1939 she had profuse colostrum from the third month on. She nursed for eight months with heavy secretion at all times and required seven weeks to dry up breasts on weaning. With her present pregnancy she also had the same leakage of colostrum from the third month on.

Dosage was started thirty-three hours after delivery, at which time her breasts were already congested, somewhat tender, and with profuse secretion of milk. Three hundred and fifty milligrams of methyl testosterone were given over a period of forty-eight hours. The congestion and tenderness disappeared by the time the treatment was stopped but secretion persisted heavily for seven days. On the eighth post-partum day, another 150 mg. were given with resultant cessation of all lactation within forty-eight hours. Since the prime purpose of the medication was to suppress lactation, we overlook the relief from discomfort in this case and rate her as a "poor" result.

As a contrast to these above "poor results" several of the more interesting of the "successful" cases are worthy of detailed description.

CASE 1.—Patient was a 30-year-old gravida ii, para ii who developed severe congestion and a right-sided breast abscess after delivery two years ago. In the present instance her baby was taken off breast four days after delivery. At that time her breasts were congested, tender, and actively secreting. She was given methyl testosterone, 50 mg. every three hours for 4 doses on the fourth post-partum day and 30 mg. t.i.d. on the fifth day. Total dosage was 290 mg. The breasts remained congested and secreting for twenty-four hours after cessation of medication and then rapidly became decongested and nontender. Forty-eight hours after treatment she was entirely comfortable, and there was no longer any secretion of milk.

CASE 3.—Patient was a 29-year-old gravida ii, para ii whose first pregnancy terminated in a stillbirth. The usual methods to suppress lactation were instituted at that time but her breasts remained swollen, tender, and actively secreting for three weeks after delivery. This finally resulted in a leftsided breast abscess and two episodes of incision and drainage. Her second pregnancy, despite a negative Wassermann, also terminated in the delivery of a macerated, stillborn infant. Starting thirty hours after delivery, she was given 30 mg. of methyl testosterone every three hours for 5 doses and then on the following day, 20 mg. every three hours for 5 doses. Total dosage was 250 mg. Her breasts remained soft, nontender and nonsecreting, throughout the entire puerperium.

CASE 4.—This case is also worthy of description. She was a 34-year-old gravida iii, para ii delivered on the private service of Sloane Hospital. After her previous delivery, two years ago, she nursed her baby for one week and then attempted to wean it because of inverted nipples. Lactorrhea developed and persisted for almost a whole year despite several courses of $MgSO_4$ administration with restriction of fluids, binders, etc. During this period of time there were several flare-ups of bilateral mastitis. With the latest pregnancy, excessive lactorrhea developed on the third post-partum day and again, despite epsom salts, tight breastbinders and restricted fluids, the breasts remained tender, congested, and over-actively secreting. Since she again had inverted nipples, her infant was not allowed to nurse. The secretion of milk was so active that fresh towels were required every two or three hours to absorb the overflow. Methyl testosterone was started on the twelfth post-partum day. Forty milligrams were given every three hours for four doses and on the following day 30 mg. every three hours for 5 doses. The total dosage, given over a period of thirty-six hours, was 300 mg. The breasts were distinctly softer by the evening of the second day of treatment and the secretion of milk was reduced by 50 per cent. Forty-eight hours after the cessation of treatment, the breasts were found to be only slightly congested and the flow of milk reduced by 75 per cent. She was discharged that evening, and we were later informed by her private physician that lactation had ceased completely on the fourth day after cessation of treatment.

CASE 13.—Patient was a 37-year-old gravida ii, para ii whose first baby was stillborn. She was treated at that time with epsom salts, breastbinders, and restricted fluids. However, her breasts remained congested, tender, and actively secreting for three weeks after delivery. Following her latest delivery, methyl testosterone was started thirty-six hours post partum. The dosage given was 50 mg. every four hours for 4 doses for a total of 200 mg. There was very mild congestion for twenty-four hours after cessation of treatment but at no time was there any secretion of colostrum or milk and absolutely no discomfort.

DOSAGE

The average case received 30 mg. of methyl testosterone every three hours for 5 doses, starting thirty-six hours after delivery and continuing the following day with 20 mg. every three hours for 5 doses; total $150 + 100 = 250$ mg.

Some patients were given 50 mg. t.i.d. for 3 doses, starting thirty-six hours after delivery and then 30 mg. t.i.d. on the next day, making 290 mg.

Other patients did well on 50 mg. every three hours for 4 doses, making 200 mg.

CONTROL

Eight control cases were run. These patients received no medication at all. They all developed congestion, secretion, and discomfort, lasting from three to seven days post partum and requiring breastbinders, ice caps, restriction of fluids, codeine, and other sedatives.

CONCLUSIONS

Methyl testosterone, in adequate dosage and given at the proper time, is of definite value in the post-partum inhibition of lactation. It brings about "drying-up" of the breasts with a minimal amount of discomfort to the patient since its oral administration removes the necessity for hypodermic injection.

The optimal dosage is about 250 to 300 mg. in divided doses over a period of thirty-six hours and starting about thirty-six hours after delivery. It may also be administered after the actual onset of secretion with beneficial results.

There were no associated symptoms of intolerance.

None of the patients treated required purging with epsom salts, tight breastbinders, icecaps, sedatives, or the limitation of fluids, milk, butter, or cream.

All patients, even those rated "poor," agreed that they were more comfortable with this form of treatment than during their earlier pregnancies when the "old-fashioned way" of drying up the breasts by use of Epsom salts, breastbinders, icecaps, and restriction of fluids, was used.

The puerperium was otherwise unaffected by the medication and on follow-up visit in the post-partum clinic the menstrual periods of these women were found to have returned "normally."

Endometrial studies on these cases are now being carried on to determine whether methyl testosterone has any effect on the subsequent menstrual cycles.

The author wishes to thank Professor Benjamin P. Watson, Director of the Sloane Hospital for Women, for his constructive criticism and for permission to carry on this work.

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CAFFEINE AS AN AID TO SODIUM PENTOBARBITAL ANALGESIA IN LABOR

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THE search for the ideal drug or combination of drugs for obstetric analgesia and amnesia has been long and arduous. It has been stated that the proper drugs have not been discovered. In recent years however, the barbiturates have given promise of fulfilling the varied requirements for ideal effect. Sodium pentobarbital in particular seems to be the most likely of the many preparations that have been tried. Nevertheless, and notwithstanding many clinical studies which emphasize the favorable results attained by the use of sodium pentobarbital alone or in combination, there still remain certain objectionable features, viz.: the confusion, restlessness, and maniacal states which this drug may cause. In the most recent review of the progress of the barbiturates in obstetric analgesia, Hellman[1] points out that "the chief objection to all analgesia technics has been, and remains today, the excitatory action of the drugs. . . . The future development of obstetric analgesia seems to depend on the discovery of compounds whose action is less excitant and whose effects are more controllable."

Since experiments with new and different barbiturates have not been promising, another combination of drugs was sought. At the suggestion of the late Dr. Bernard Fantus, to whom the objectionable features of sodium pentobarbital analgesia were outlined, we decided to add caffeine, a mild cerebral stimulant, to the drug. Thus the delirium of the mother which may be due to a cutting-off of the control of the voluntary cerebral impulses might be counteracted by the mild cerebral stimulation of caffeine. The purpose of this paper is to report the results of these experiments. While the number of cases is not large, it is a well-selected and controlled group and reflects the valuable contributory action of this cerebral stimulant; it also intimates that other, more powerful, cerebral stimulants might be valuable adjuncts. We hope that it will open new vistas into the future progress of obstetric analgesia.

METHOD EMPLOYED

In our series the cases were carefully selected from patients having normal labor. The medication was given only to women who had cephalic presentations and who had no complications of toxemia, hypertension, or other medical disease. It was not given to elderly multiparas who had had many and easy deliveries. The analgesia was not administered until the patient was definitely in labor with a 3 to 4 cm. dilatation of the cervix. The initial dose of sodium pentobarbital was 7½ gr.; and additional 3 gr. were given in four to five hours, or whenever the effect, by observation, was wearing off. The largest dose given was 13½ gr.; most patients (89 per cent) received a dosage of 7½ gr. Caffeine citrate in doses of 5 gr. was also administered orally together

with the sodium pentobarbital and was repeated every hour or two in accordance with the excitability of the patient. Occasionally it was given subcutaneously during the second stage of labor when a more immediate action was required. The largest dose given was 35 gr.; the average was 12.6 gr.

In this study a total of 332 patients were observed. They were divided into three groups, as follows: one series of 146 patients were observed in consecutive admission to the normal labor ward who received no medication at all; 60 patients were placed on the control series receiving only the prescribed dosage of sodium pentobarbital, but no caffeine; the final group of 116 patients received both the sodium pentobarbital and caffeine. Table I illustrates their average age, percentage of primigravidas in each group, and average parity of multiparas in each group.

TABLE I

	NO. OF PATIENTS	AVERAGE AGE	% OF PRIMIPARAS	AVER. PARITY OF MULTIPARAS
No medication	146	23½	50	3.5
Sodium pentobarbital	60	22½	50	2.66
Sodium pentobarbital and caffeine	116	22	69	2.63

A special nurse was in constant attendance throughout the course of labor after administration of the drug. Occasionally, the labor would last longer than a twenty-four-hour period. The conduct of such a case was then turned over to the special regime followed at the Cook County Hospital for prolonged labor. However, these cases were not dropped from our series. The longest labor was 57½ hours. There was no deviation in management when the patient was ready for delivery. Supplemental anesthesia was given when needed. Spontaneous delivery was allowed to occur if possible; low forceps was the only operation necessary to deliver patients on sodium pentobarbital medication. The infant was cared for in the usual manner. After delivery sleep usually ensued quickly, although occasionally, a patient would require additional close watching for an hour or two. The following day she would be questioned regarding amnesia and analgesia.

RESULTS

In any discussion of the effects of an obstetric analgesic and amnesic the following maternal and fetal factors must be considered: changes in blood pressure, pulse, temperature, and respirations, excitability and cooperation (with which, perhaps, the toxicity is closely related), changes in length of labor, operative incidence, blood loss, and post-partum morbidity, the amount of supplemental anesthesia necessary, the amount of post-partum sleep, the degree of amnesia and analgesia, the fetal narcosis and mortality, and any evidence of delayed effects on the infant.

As far as blood pressure, pulse, temperature, or respirations were concerned, no unusual or characteristic variations were noted during the course of this study. The abscence of any rise in blood pressure is consistent with the findings of Ross[2] who used the drug therapeutically in the late toxemias of pregnancy. The absence of marked respiratory

depression may be due to the effect of the caffeine counteracting this property of barbiturate medication and the possibility of sudden respiratory collapse or atelectasis as discussed by Cheatham,[3] Sheldon,[4] and Willcox.[5]

The patient's excitability and cooperation were judged by one of two nurses in constant attendance who were exclusively employed on all these cases throughout our study. Cooperation was defined as the ability of the patient to answer to, and to perform, spoken commands by the attending doctor or nurse. A comparison of the results obtained with and without the use of caffeine may be obtained from Table II. When these two groups are compared with each other (not with the total, as recorded), a much higher incidence (18 per cent more) of excellent cooperation and lower incidence of only fair (40 per cent less) and poor (17 per cent less) cooperation is obtained from patients who received caffeine. It is hoped that the use of caffeine and other cerebral stimulants in combination with sodium pentobarbital in a larger series of cases and by other observers will serve to point out, even more markedly, its clinical effect in the allayment of excitability and increase in cooperation of the patient.

After a statistical analysis of the length of the various stages and also of the total length of labor (Table II), the only significant difference noted was the shorter labor of the multiparas receiving no medication. No completely adequate explanation is offered for this occurrence other

TABLE II. COMPARISON OF MATERNAL AND FETAL FACTORS

	SODIUM PENTOBARBITAL		SODIUM PENTOBARBITAL WITH CAFFEINE		NO MEDICATION	
	NO. OF CASES	% OF CASES	NO. OF CASES	% OF CASES	NO. OF CASES	% OF CASES
Cooperation:						
Excellent	32	53.3	70	63.0		
Good	10	16.7	17	15.4		
Fair	9	15.0	10	9.0		
Poor	9	15.0	14	12.5		
Total length of labor:						
Primiparas		11.54 hr.		11.85 hr.		12.14 hr.
Multiparas		9.94 hr.		9.37 hr.		7.45 hr.
Operation:						
Low forceps	5	8.3	17	15.0	5	3.5
Midforceps	0	0	0	0.0	2	1.5
Morbidity*	2	3.3	3	2.6	†	3.1
Amnesia:						
Excellent	50	83.4	88	78.0		
Fair	9	15.0	22	19.5		
Poor	1	1.6	3	2.5		
Narcosis of infant:						
None	46	77.0	95	84.1	143	98.0
Sleepy	11	18.0	13	11.5	1	0.7
Deep	3	5.0	5	4.4	2	1.4

*Corrected morbidity.

†Based on morbidity for the entire year (1940) for the normal labor ward (3,535 patients).

than the fact that these patients had a much higher average parity (Table I), resulting, possibly, in easier labors.

In accordance with Galloway and Smith[6] and Gruber,[7] we noted an increase in the operative incidence. However, the low forceps operation was the only interference necessary in all the patients receiving medication. Since the operation of "prophylactic forceps" is not practiced as a routine procedure on all primiparous patients at the Cook County Hospital, the increased incidence of low forceps operations on those women receiving sodium pentobarbital with and without caffeine can be more truly appreciated. We can find no reason to explain this increased incidence in patients receiving caffeine over those who did not receive this drug. The relatively greater number of low forceps operations were satisfactorily performed under local and block anesthetic methods, and there was no material increase in the amount of supplemental inhalation anesthesia necessary in patients receiving sodium pentobarbital medication. No appreciable increase or decrease in the amount of blood loss was noted in any of the comparative series. In spite of the increased operative incidence in all patients given the barbiturate medication, the post-partum morbidity remained constant (Table II).

After delivery the patients were placed in bed, restrained with a sheet across the chest and watched for a short period of time until sleep ensued. Only in one or two instances did a period of excitement last for an hour or two after delivery. The post-partum sleep usually lasted from eight to twelve hours. The following day the patients were questioned in regard to amnesia and analgesia. The results are recorded in Table II. It should be remembered that amnesia is entirely a subjective symptom. The percentage of those patients receiving excellent amnesia was only slightly higher among those not receiving caffeine (83.4 per cent) than among those who did receive this drug (78 per cent). This is not surprising in view of the fact that caffeine is a cerebral stimulant.

A comparison of the fetal narcosis reveals that 85 per cent of the babies delivered of mothers who also received caffeine had no narcosis, while 77 per cent of the babies from mothers who had no caffeine had no narcosis. While this difference is not too striking, we feel that it is a definite indication of a step toward reducing fetal narcosis in obstetric analgesia. The exact mechanism of this aid is not completely understood. Perhaps the caffeine likewise stimulates the fetal respiratory center, as well as the maternal cerebral centers. None of the babies in any of our comparative series died and none showed any delayed effects of the drugs at the time the mother was sent home from the hospital. The most recent articles by Henderson and associates[8] and by McCormick[9] tend to show that there is a high degree of general safety and security with well-handled analgesics. They claim that when properly supervised and in the hands of those familiar with their use, analgesics per se do not increase the incidence of asphyxia. McCormick[9] also states that "by eliminating the 'physiologic weight loss' (which, he claims, is a manifestation of birth shock) and enhancing the fetal and neonatal welfare, wisely used obstetric analgesia is no longer a privilege but a prerequisite of better obstetrics."

While the results of this study are only indicative, still we feel that, clinically, it is a step in the right direction and warrants further experimentation with larger doses and more powerful cerebral stimulants. The use of coramine and other drugs is suggested.

SUMMARY AND CONCLUSIONS

A comparative study of the effect of caffeine upon sodium pentobarbital analgesia in labor has been made using two groups of patients as controls. One control group received no medication at all; the other received sodium pentobarbital, but no caffeine.

1. Parturient women given sodium pentobarbital with caffeine manifest little, if any, decrease in respiratory rate. The caffeine may counteract the respiratory depression of the barbiturate medication.

2. The addition of caffeine to sodium pentobarbital medication increases the cooperation and lessens the excitability of the parturient patient.

3. Sodium pentobarbital, with or without caffeine, increases the length of labor in multiparas a moderate amount, but these results are indeterminate.

4. No operative procedure other than low forceps was necessary to deliver any patient receiving sodium pentobarbital. However, a larger percentage of those who received caffeine required the low forceps delivery than those who did not receive this drug.

5. In spite of the fact that the operative incidence was increased in all patients receiving sodium pentobarbital medication, the post-partum morbidity was not increased. None of our patients died.

6. Although caffeine stimulates the cerebrum, its addition to sodium pentobarbital caused only slight decrease in the number of patients obtaining excellent post-partum amnesia.

7. A somewhat higher percentage of infants delivered of mothers who received caffeine with the sodium pentobarbital medication showed no narcosis. The exact mechanism of this process is not completely understood; it is possible that the caffeine may stimulate the fetal respiratory center.

8. Clinically we feel that the addition of caffeine constitutes a step in the right direction toward better obstetric analgesia and warrants further work with other drugs.

We wish to extend our sincere appreciation to Dr. Robert B. Lewy and to Miss Elizabeth M. Adles of the Department of Therapeutics for their splendid cooperation, helpful suggestions, and constructive criticism throughout the course of this study. Our thanks are also tendered to Miss Elaine Redding and Miss Helen Watson, our two nurses, for their constant and courteous service.

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BRENNER TUMOR OF THE OVARY ASSOCIATED WITH UTERINE BLEEDING

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THIS report of a Brenner tumor of the ovary is of unusual interest because it occurred in a patient 77 years of age and was associated with symptoms usually ascribed to tumors having an estrogenic endocrinal function, viz., vaginal bleeding and hyperplastic proliferative endometrium.

CASE REPORT

Mrs. F. S., aged 77 years, white, widow, was admitted to hospital on Oct. 3, 1940, with history of recurrent painless vaginal bleeding which occurred for the first time on Dec. 17, 1938, and persisted for three days. There was recurrence of the bleeding nine days later for three days. From January, 1939, to June, 1940, she bled only twice, each time the bleeding lasting one day. The last bleeding occurred Sept. 4, 1940. With the onset of the vaginal bleeding, a definite increase in size of both breasts was noted. Just prior to hospital admission, an endometrial biopsy was obtained, which revealed hyperplastic endometrial glands similar to those seen in hyperactive or persistent proliferative endometrium.

Menarche began at the age of twelve years and the interval of menstruation was twenty-one days with flow, which was always profuse, lasting four days. There was mild dysmenorrhea the first and last days of the flow. Menopause occurred at age 48 and was not accompanied by any unusual symptoms.

Pertinent findings in the physical examination were: mild generalized arteriosclerosis with moderate hypertension and nontoxic adenoma of the right lobe of the thyroid gland. Upon vaginal examination, rugae were present; the vagina was moist and spacious without tears or relaxations; the cervix was normal in size and appearance; the uterus was anterior, smooth, and of normal size for a menstruating woman. Posterior to the uterus, there was a cystic, fixed mass arising from the region of the left ovary. This was approximately 8 cm. in diameter.

At operation on Oct. 4, 1940, a dilatation and curettage were performed, with recovery of a small amount of endometrial tissue. The uterus was smooth, soft and approximately the size of a five to six weeks' pregnancy. The right ovary was 1 by 0.5 by 0.5 cm. and was entirely sclerotic. There were no visible Graafian follicles. Arising from the left ovary and dropping into the cul-de-sac posteriorly, there was a cystic tumor 8 cm. in diameter with a solid area in its wall. Left oophorectomy was performed.

Pathologic Findings.—Specimen (office endometrial biopsy) consisted of a small amount of curetted tissue in narrow strips.

Microscopic Description: Microscopic sections of the tissue revealed endometrium. The surface epithelium was high columnar in type with

nuclei situated at the bases of the cells. The nuclei were slightly hyperchromatic. The glands were simple tubular in type with high columnar epithelium and with nuclei situated at the bases of the cells, for the most part. A few of the glands had atrophic epithelium and were mildly cystic. The cytogenic stroma contained fairly large cells with hyperchromatic nuclei and was only moderately compact. The general appearance was that of endometrium at the eighth to tenth day of a normal twenty-eight-day menstrual cycle.

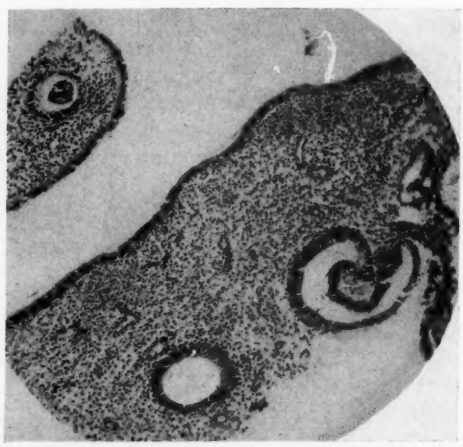

Fig. 1.—Photomicrograph of biopsy of endometrium revealing glands and stroma in proliferative phase of the menstrual cycle. (H. & E. stain, ×100.)

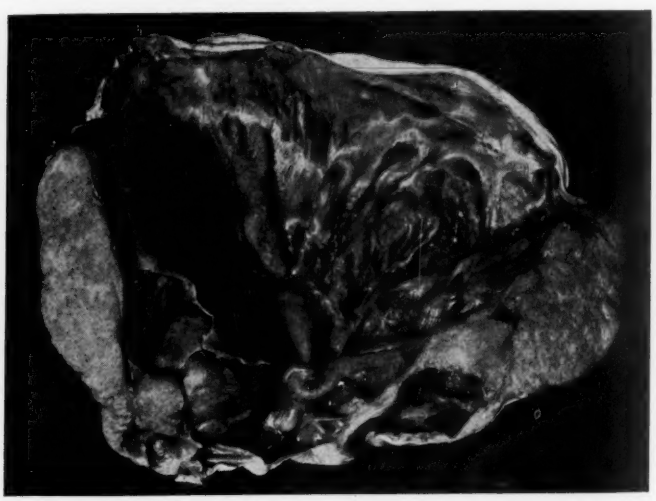

Fig. 2.—Photograph of gross specimen. Multilocular pseudomucinous cystadenoma with Brenner tumor in wall of cyst. The Brenner tumor is seen as the solid white area in the cyst wall.

Microscopic Diagnosis: Slight hyperplastic, persistent proliferative endometrium.

Tissue Removed at Operation in Hospital (Oct. 4, 1940).—*Gross Description:* Specimen consisted of a minute amount of uterine curettings

and a cystic tumor of the left ovary. The uterine curettings presented no special characteristics. The specimen of the cystic tumor was nearly spherical in shape and measured 12 by 8 by 8 cm. The outer wall was smooth. It was white to blue in color and the vessels were prominently

Fig. 3.—Photomicrograph of wall of pseudomucinous cyst revealing mucus-producing epithelium and glands supported by fibrous stroma. (H. & E. stain, ×100.)

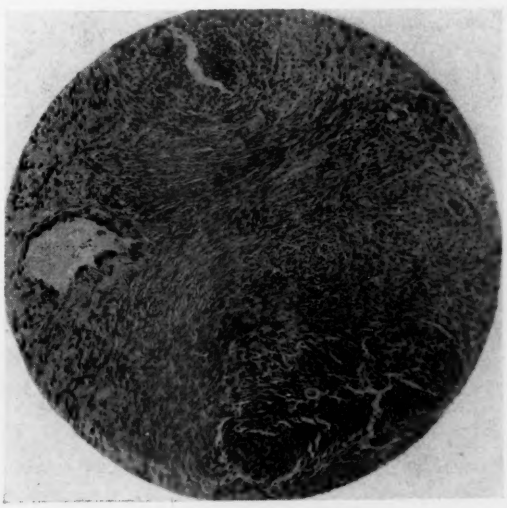

Fig. 4.—Photomicrograph from solid area of cyst wall revealing typical Brenner tumor structure, consisting of interlacing growth of dense fibrous connective tissue and islands of epithelium, the so-called Walthard's rests. (H. & E., ×100.)

displayed on its surface. The contents were colorless, clear, thin, slightly mucinous fluid. Upon section the cyst was found to be multilocular, the largest locule being 8 cm. in diameter. There were four other locules which were definite and measured from 2 to 5 cm. in diameter. There were no papillary projections upon the internal wall, the wall being

smooth and white to pink in color. Vascular markings were also prominent. Growing from the inner wall of the larger locule, a large, solid, very firm, slightly rounded tumor mass, which measured 6 by 5.5 by 2.5 cm., was found. The color of the mass was white to yellow. The cut surface was coarsely fasciculated by interlacing bundles of tissue.

Microscopic Description: Microscopic sections of the cyst wall stained by hematoxylin-eosin revealed it to be lined by simple columnar epithelium. Nuclei were basal. The borders of the epithelial cells were faintly stained or clear, representing mucus content. The supporting tissue of the cyst was of loose fibrous connective tissue type. Microscopic sections taken from the solid tumor stained by hematoxylin-eosin revealed dense interlacing bundles of mature fibrous connective tissue which contained nests of epithelial cells. The cytoplasm of the epithelial cells was fairly abundant and pale staining. The nuclei were pale or slightly vesicular. The epithelial cell masses were sharply circumscribed from the surrounding connective tissue and had the general appearance of Walthard inclusions as found normally about the Fallopian tube and ovary. Occasionally, there were small cystic cavities in the centers of the epithelial masses. There were no mitotic figures in any part of the tumor or the cyst wall.

Microscopic Diagnosis: Multilocular, nonpapillary, pseudomucinous cystadenoma with Brenner tumor in wall of cyst (left ovary).

DISCUSSION

Brenner tumors fall into two well-defined groups. They are either solid tumors resembling fibromas, or pseudomucinous cystomas in the walls of which the Brenner tumor stands out as a solid nodule. There are great variations in the size of the tumor. Some are of microscopic size, while others may become very large even when not associated with cystomas. The gross appearance of the solid tumors is quite similar to that of a fibroma, although there is frequently a yellowish tint to the cut surface. There is only slight tendency to necrosis and hemorrhage but cystic degeneration is more common, in the solid variety. No definite capsule exists, although the surrounding ovarian stroma is more or less compressed.

Microscopically, there are scattered cell groups lying in a superabundant fibrous stroma. The cell groups are compact and the cells may be polyhedral, cubical, cylindrical, rarely ciliated and occasionally stratified. Small cysts are frequently formed from degeneration of the compact cell masses. Glycogen is present in the cells. Fat is absent. The stroma, which comprises the bulk of the tumor, is composed of spindle cells with collagen fibrils and is frequently hyalinized.

There are three theories as to the histogenesis of the tumor. Robert Meyer[1] believed that the tumor arose from islands of indifferent cells in the ovary first fully described by Walthard[2] and since called Walthard inclusions. These are found in the superficial portion of the ovary or, frequently, in the uterine tubes and uterine ligaments, especially in the newborn and young child, but also in the adult. They consist of nests of cells resembling squamous epithelium or transitional, often showing cystic cavitation, or actually converted into tiny cysts, or the inclusions may take the form of glandlike spaces lined by columnar or ciliated epithelium, with at times definite mucus formation. Schiller's[3] theory was postulated on a dislocation of cells from a primitive urogenital con-

nection. A third theory considers that the tumors are one-sided developments of teratomas. This is based on the occasional association with pseudomucinous cystomas, which also are regarded as one-sided developments of teratomas by certain investigators.

Clinically the tumor is benign and slowly growing. Sixty per cent occur after the menopause. In the literature the oldest patient reported with a Brenner tumor was aged 71, and the youngest aged 25 (Novak[4]). In the majority of reports the tumors were an incidental finding to other pathologic changes of the female generative organs.

Practically all observers who have written about the Brenner tumor say that there is no endocrine effect produced by the tumor.[5-7] Novak[4] reported one case of postmenopausal bleeding associated with a Brenner tumor. The endometrium was not studied, and he does not think the bleeding was related to the presence of the tumor. Postmenopausal bleeding is said to have occurred in a number of other cases in which the endometrium was not studied. Novak further stated that in spite of this, there is no reason to think that the bleeding was due to any direct endocrine effect upon the uterus. Usually, the uterus in elderly women with Brenner tumor has been described as senile and atrophic.

Fauvet[8] reported 4 cases of Brenner tumor, 3 of which presented postmenopausal bleeding. Two of the 3 cases exhibited polypoid endometrium. He concluded that there is neither clinical nor microscopic evidence that the Brenner tumor is the source of hormonic reactivating or rejuvenating substances; however, he thought it may be attributed to extragenital endocrine stimuli, possibly from the adrenal cortex.

Schiffman[9] reported endometrial hyperplasia and uterine bleeding in association with a Brenner tumor.

TeLinde[10] cited a case of Brenner tumor in a woman aged 62 who exhibited profuse recurrent postmenopausal bleeding, diabetes and hypertrichosis. She had a tumor replacing the right ovary and adenocarcinoma of the endometrium.

In a later communication, TeLinde[11] listed the Brenner tumor as one of a group of tumors associated with postmenopausal bleeding.

In any analysis of postmenopausal bleeding, it will be found that pseudomucinous cystomas have been found to be associated in a small percentage of cases with hyperplasia of the endometrium. Taylor[12] in a recent review believed that endometrial hyperplasia associated with a pseudomucinous cystoma may be the result of a general hyperemia in the pelvis from the presence of the tumor or possibly also the result of substances elaborated by the cysts or by activated ovarian cells in the walls of the cysts. Therefore, it would not be unusual that the Brenner tumor possessed the ability to initiate uterine bleeding, since some are associated with pseudomucinous cystomas.

Our case exhibited effects usually attributed to the estrogens, such as vaginal bleeding, breast development, a good-sized uterus, normally appearing cervix, spacious vagina, and rugae with a hyperplastic proliferative type of endometrium. Thus, more evidence than vaginal bleeding alone is offered in support of the theory that the tumor was hormonally active. Vaginal bleeding alone without supporting evidence should probably be taken only as a sign of pelvic congestion. Estrogens administered to ovariectomized animals and women will produce the changes which were observed in our patient.[13]

Postmenopausal bleeding in the absence of uterine pathologic changes must be considered as a form of menstruation. It is now accepted that the menses are probably degenerative but depend upon endocrine factors whose activity has preceded the onset of bleeding. These factors apparently need not include corpus luteum hormone (as in the anovulatory cycles), therefore, estrogens alone may be sufficient to explain the essential mechanism of menstruation.[14] Assay for estrogens would probably have decided the matter in our case, but unfortunately this was not done.

One theory of origin of the tumor favors the hypothesis that the Brenner tumor may be hormonally active, since it is related to an early undifferentiated phase of genital development. It may be argued that the cells of the tumor may function along female lines in certain cases.

Goodall[15] says that embryonic rests in the ovary may remain dormant for all time or may be awakened into activity by any one of many stimuli at any age. Many, if not all, of these rests are aroused to proliferation as a result of nutritional changes. These changes may be primary vascular or neurotrophic. The nutritional influence may operate by stimulation of the normal ovarian function to abnormal development or by stimulation of the abnormal embryonic rests in the ovary to pathologic activity and sometimes to unbridled aberrant growth.

CONCLUSION

Estrogenic hormone production is not definitely excluded as a biologic function of a Brenner tumor, since in this case, the tumor occurred in a 77-year-old woman and many of the anatomic and physiologic changes usually associated with the presence of estrogens were found.

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THE USE OF QUICK FREEZING METHODS IN GYNECOLOGIC PRACTICE

A Preliminary Report

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LIKE thermotherapy, cryotherapy, or the treatment with cold, may be divided into two types: in one cold is applied in such a way that no damage is inflicted on the cellular structures; in the other the integrity of such structures is destroyed. Cold compresses and ice bags are extensively employed for the relief of pain in acute and chronic inflammatory processes, and satisfactory local anesthesia has been obtained through the use of the ethyl chloride spray. Solid carbon dioxide and liquid oxygen have been used for the destruction of pathologic growth in various fields of medicine, including gynecology.

Pusey[1] published the first report in 1907, on the successful treatment of cutaneous disorders with solid carbon dioxide. In 1927 and 1928 Kroh[2] reported a series of more than 900 cases of various cutaneous disorders, including furuncles and carbuncles, in which treatment with solid carbon dioxide was used. He expressed the belief that the results of such treatment were better than those obtained with radium therapy, because the scars stayed pliable, were not contractile, and displayed no tendency to keloid formation.

In 1930 Lortat-Jacobs and Solente[3] reported their results from the use of the cryocautere, an instrument consisting of a container and a rodlike applicator filled with a mixture of solid carbon dioxide and acetone. On the basis of biopsies they concluded that the results from using this instrument in the treatment of chronic endocervicitis and erosions of the cervix were superior to those obtained with the electric cautery, since after treatment there was complete regeneration of the mucous lining without contractile scars. The chief objections to their instrument are the size of the freezing mixture container, which reduces visibility and the limited time of application of cold.

More recently, Weitzner[4] reported excellent results from the use of solid carbon dioxide in 325 cases of cervical erosions and endocervicitis. From biopsies, which were performed in 111 cases, he discovered that as early as seven days after treatment epithelial proliferation resembling carcinoma was present in 30 per cent of the cases. This observation prompted him to discontinue treatment for one year and to investigate further the changes taking place in the healed lesions of the cervix, which macroscopically appeared smooth and normal. The pseudocarcinomatous proliferation was present for from three months to two and one-half years before it disappeared. He concluded that these observations substantiated those of Berenblum,[5] who in 1929 and in 1930 had carried out similar studies and had expressed the opinion that

cryotherapy has no carcinogenic effect and that the proliferation merely represented increased activity of the healing epithelium.

In a paper published in 1939, Smith and Fay[6] pointed out that there is a critical temperature below which young undifferentiated cells become inactive and undergo degeneration. They discovered that the lowest temperature at which healthy mature cells may be kept intact is about +40° F. These investigators actually employed not slow freezing but only cooling of the tissues, a method which differs essentially from quick freezing, in which the tissues are momentarily exposed to extremely low temperatures.

Notwithstanding the excellent results obtained with quick freezing, this method of treatment has not gained the place it deserves in the medical armamentarium. The explanation for this lies in the nature of the instruments available for the application of cold, for they are satisfactory only for applications to exposed areas. One major objection to using these instruments in body cavities has been the difficulty of removing the applicator once the tissue has been frozen. Consequently, it occurred to me that, if a more practical means of applying cold were devised, cryotherapy might gain the wider place it deserves. With this end in view an apparatus* has been developed which, it is believed, overcomes the disadvantages of its predecessors. The basic operating principle is the same as that of the electric refrigerator as is evident from Fig. 1.

APPARATUS

The refrigerant medium used in the apparatus is Freon gas, or dichlorodifluoromethane (CF_2Cl_2). This gas was chosen because it is nonexplosive, noninflammable, and nonpoisonous. By circulating this gas under a pressure of 100 pounds (45.5 kg.) an even temperature of –40° F. can be maintained. Dr. Fay and coworkers,[7] who are at present experimenting with this apparatus, have obtained temperatures of –6° to –8° F. within the tissues at the time the frosting started on the surface, determined by means of a thermocouple. This, in their opinion, is well within the range of effectual therapy.

One of the most important advantages of the apparatus is its defrosting device, which facilitates the removal of the applicator from the frozen tissue. Simply by short-circuiting and returning the expanded and heated gas, under low pressure, into the expansion chamber, the applicator is defrosted and easily removed.

The instrument is equipped with an electric sterilizer and an automatic stop clock, which facilitates the administration of treatment for a predetermined length of time. The three permanently attached applicators are designed for gynecologic therapy; two, of different sizes, are intended for straight insertion into the cervical canal and the third for flat application to the cervix.

CLINICAL OBSERVATIONS

We have used this instrument in 60 cases in which there was a diagnosis of chronic endocervicitis, cervical erosion or cervical polyp, singly or in combination. Data for these cases are given in Table I.

*Made by Peerless of America, Marian, Ind.

Twenty-three cases were treated for erosion of the cervix, 18 for endocervicitis, 13 for erosion associated with endocervicitis, 2 for cervical polyp, 3 for cervical polyp associated with erosion, and 1 for multiple cervical polyps associated with erosion and endocervicitis. The average number of treatments was 1.58 and the average time for the cervical

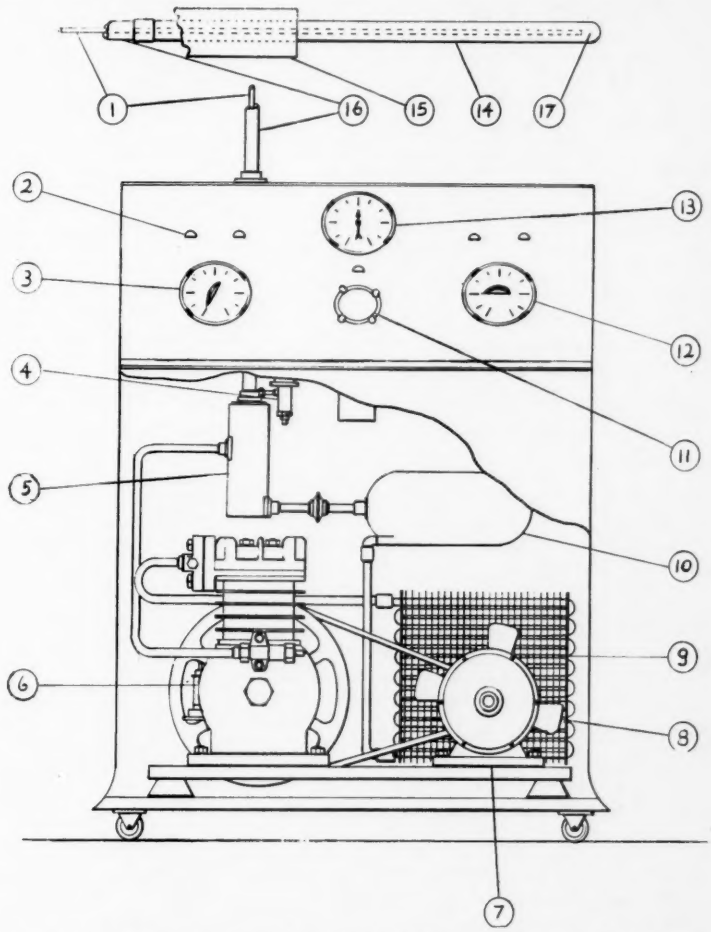

Fig. 1.—*1*, Liquid line; *2*, control indicator lights; *3*, switch and time control for length of freezing; *4*, thermostatic control; *5*, distribution chamber; *6*, pump and compressor; *7*, motor; *8*, fan for condensor; *9*, condensor; *10*, receiver tank; *11*, sterilizer for applicators; *12*, defrosting switch; *13*, sterilizer switch; *14*, applicator (straight); *15*, rubber insulator; *16*, suction tube; *17*, expansion chamber.

By turning switch (*3*), motor (*7*) is started, pumping refrigerant from receiver tank (*10*) into distribution chamber (*5*) with thermostatic control (*4*) and through liquid line (*1*) into expansion chamber (*17*) in applicator (*14*), then returning refrigerant through suction tube (*16*) into compressor (*6*) and into condensor (*9*), cooled by fan (*8*) and back into receiver tank (*10*), thus completing a full cycle. Defrosting switch (*13*) returns heated refrigerant into expansion chamber (*17*). Switch (*12*) starts sterilizer (11). Control lights (*2*) are flashed by turning switches (*3*, *12*, *13*) indicating operation of freezing, defrosting and sterilizing, respectively.

For the sake of simplicity only one applicator is shown. The applicators are insulated with hard rubber tubings (*15*).

The machine is mounted on rubber wheels, weighs 165 pounds, and has a forward sloping instrument panel. Base measures 43 by 43 cm., height in front 69 cm., in rear 80 cm. The flat applicator is 20 cm. long. The circular surface for freezing has a diameter of 2 cm. The straight applicators are 25 cm. long, with a width of 8 and 5 mm., respectively, and have removable hard rubber insulators.

TABLE I. RECORD OF CASES

CASE	AGE	GRAV.	DIAGNOSIS	DATE	TIME OF APPLICATION MIN.	TYPE OF APPLICATION	LAST EXAM.	RESULT
1	31	0	Endocervicitis	12/ 6/39	3	Intracerv. 6 cm.	3/ 7/40	Healed
				2/ 4/40	6	Intracerv. 6 cm.		
2	25	i	Endocervicitis	1/23/40	6	Intracerv. 6 cm.	2/29/40	Healed
3	39	0	Endocervicitis	1/24/40	3	Intracerv. 6 cm.	4/ 5/40	Healed
				2/22/40	6	Intracerv. 6 cm.		
4	24	iii	Large erosion	3/15/40	5	Intracerv. 3 cm.	4/30/40	Healed
				4/12/40	5	Intracerv. 3 cm.		
5	23	i	Small erosion	4/12/40	6	Intracerv. 3 cm.	6/ 7/40	Healed
6	22	ii	Small erosion	5/13/40	8	Intracerv. 3 cm.	6/ 7/40	Healed
7	44	i	Papill. erosion	7/ 7/40	6	Intracerv. 6 cm.	11/20/40	Healed
			Multiple polyps	7/ 7/40	6	Flat to cervix		
				7/29/40	10	Intracerv. 6 cm.		
			Endocervicitis	11/14/40	5	Intracerv. 6 cm.		
8	47	ii	Small erosion Endocervicitis	8/ 7/40	6	Intracerv. 3 cm.	9/28/40	Healed
9	26	ii	Large erosion	8/24/40	6	Intracerv. 6 cm.	1/ 5/41	Healed
			Endocervicitis	8/24/40	3	Flat to cervix		
				11/ 2/40	8	Intracerv. 6 cm.		
10	41	i	Endocervicitis (Retroversion)	9/19/40	10	Intracerv. 6 cm.	3/29/41	Unchanged
				11/14/40	3	Intracerv. 6 cm.		
11	29	ii	Papill. erosion	9/19/40	3	Flat to cervix	11/ 8/40	Healed
12	24	ii	Large erosion	9/28/40	7	Intracerv. 6 cm.	2/ 1/41	Healed
			Endocervicitis	10/12/40	10	Intracerv. 6 cm.		
13	25	iii	Large erosion	10/ 5/40	10	Intracerv. 6 cm.	11/ 9/40	Unchanged
			Endocervicitis	10/ 5/40	3	Flat to cervix		
				11/ 2/40	8	Intracerv. 6 cm.		
14	33	ii	Small erosion Large polyp	10/23/40	10	Intracerv. 3 cm.	12/13/40	Healed
15	30	0	Endocervicitis	10/23/40	10	Intracerv. 6 cm.	11/19/40	Healed
16	37	0	Endocervicitis	10/23/40	6	Intracerv. 6 cm.	2/24/41	Healed
				12/23/40	1	Intracerv. 6 cm.		
				1/17/41	1	Intracerv. 6 cm.		
				1/24/41	1	Intracerv. 6 cm.		
17	29	ii	Large erosion	10/26/40	8	Intracerv. 6 cm.	2/ 1/41	Healed
			Endocervicitis	11/23/40	3	Intracerv. 6 cm.		
				11/23/40	4	Flat to cervix		
				12/28/40	2	Intracerv. 6 cm.		
				12/28/40	2	Flat to cervix		
18	33	0	Endocervicitis	10/28/40	2	Intracerv. 6 cm.	5/10/41	Healed
19	22	i	Large erosion	11/ 2/40	5	Flat to cervix	1/29/41	Healed
				11/23/40	3	Flat to cervix		
				12/29/40	3	Flat to cervix		
20	34	0	Small polyp	11/ 2/40	2	Intracerv. 3 cm.	11/24/40	Healed
21	19	0	Small erosion	11/ 2/40	2	Intracerv. 3 cm.	2/ 1/41	Healed
22	50	ii	Large polyp	11/18/40	5	Intracerv. 3 cm.	12/16/40	Healed
				11/18/40	2	Flat to cervix		
23	50	i	Endocervicitis	11/20/40	3	Intracerv. 6 cm.	12/21/40	Healed
				12/ 4/40	2	Intracerv. 6 cm.		
24	46	iv	Small erosion Endocervicitis	12/ 2/40	2	Intracerv. 6 cm.	2/ 8/41	Healed
25	27	0	Endocervicitis	12/10/40	2	Intracerv. 6 cm.	6/27/41	Healed
				1/22/41	1	Intracerv. 6 cm.		
				2/ 7/41	1	Intracerv. 6 cm.		
26	40	0	Small erosion	12/11/40	3	Flat to cervix	2/20/41	Healed
				12/26/40	3	Flat to cervix		
27	25	i	Large erosion	12/13/40	2	Flat to cervix	2/28/41	Healed
			Endocervicitis	1/ 3/41	1	Intracerv. 6 cm.		
				2/ 4/41	2	Intracerv. 6 cm.		

TABLE I—CONT'D

CASE	AGE	GRAV.	DIAGNOSIS	DATE	TIME OF APPLICATION MIN.	TYPE OF APPLICATION	LAST EXAM.	RESULT
28	43	iii	Endocervicitis	12/13/40	2	Intracerv. 6 cm.	3/24/41	Healed
29	23	ii	Small erosion	12/14/40	3	Intracerv. 6 cm.	5/12/41	Healed
			Endocervicitis	12/14/40	3	Flat to cervix		
				2/ 1/41	3	Intracerv. 6 cm.		
				2/ 1/41	3	Flat to cervix		
				3/26/41	1	Intracerv. 6 cm.		
30	28	0	Endocervicitis	12/17/40	2	Intracerv. 6 cm.	2/ 3/41	Healed
31	25	i	Large erosion	12/24/40	2	Flat to cervix	2/28/41	Healed
				1/10/41	2	Intracerv. 3 cm.		
				1/25/41	1	Intracerv. 3 cm.		
32	65	ii	Papill. erosion	12/28/40	1	Intracerv. 3 cm.		
				12/28/40	1	Flat to cervix		
				1/10/41	1	Intracerv. 3 cm.		
33	26	0	Small erosion	12/30/40	1	Intracerv. 3 cm.	3/24/41	Healed
			Endocervicitis	1/20/41	2	Intracerv. 3 cm.		
				1/27/41	2	Intracerv. 3 cm.		
34	24	i	Large erosion	1/13/41	1	Intracerv. 3 cm.	2/26/41	Healed
				1/13/41	1	Flat to cervix		
				2/13/41	2	Intracerv. 3 cm.		
35	27	i	Endocervicitis	1/14/41	2	Intracerv. 6 cm.	3/ 6/41	Healed
36	28	ii	Large erosion	1/15/41	1	Intracerv. 3 cm.	2/24/41	Healed
				1/15/41	2	Flat to cervix		
37	34	0	Endocervicitis	1/16/41	2	Intracerv. 6 cm.	3/20/41	Healed
38	27	i	Large erosion	1/17/41	1	Flat to cervix	2/21/41	Healed
				1/31/41	1	Flat to cervix		
				2/ 7/41	1	Flat to cervix		
39	26	ii	Endocervicitis	1/20/41	1	Intracerv. 6 cm.	3/ 4/41	Healed
40	35	ii	Large erosion	1/24/41	2	Flat to cervix	3/21/41	Healed
				2/ 7/41	2	Flat to cervix		
				2/21/41	1	Flat to cervix		
41	35	i	Large erosion	1/24/41	1	Flat to cervix	3/28/41	Healed
				2/14/41	1	Flat to cervix		
				3/14/41	1	Flat to cervix		
42	31	i	Endocervicitis	1/25/41	2	Intracerv. 6 cm.	3/26/41	Healed
43	36	ii	Large erosion	1/29/41	2	Flat to cervix	5/14/41	Healed
44	35	0	Small erosion	1/31/41	1	Flat to cervix	3/14/41	Healed
45	49	0	Small erosion	1/31/41	1	Intracerv. 6 cm.	5/14/41	Healed
			Endocervicitis					
46	29	0	Small erosion	2/ 4/41	2	Intracerv. 3 cm.	2/25/41	Healed
			Small polyp					
47	31	ii	Large erosion	2/ 5/41	2	Flat to cervix	3/ 8/41	Healed
48	33	0	Endocervicitis	2/ 6/41	1	Intracerv. 6 cm.	3/16/41	Healed
49	29	0	Large erosion	2/12/41	1	Flat to cervix	5/12/41	Healed
50	32	ii	Small erosion	2/12/41	2	Intracerv. 3 cm.	3/11/41	Healed
			Endocervicitis					
51	19	0	Large erosion	2/14/41	1	Flat to cervix	5/13/41	Healed
52	24	ii	Small erosion	2/17/41	1	Intracerv. 3 cm.	3/26/41	Healed
53	35	ii	Small erosion	2/20/41	4	Intracerv. 3 cm.	3/24/41	Healed
			Large polyp					
54	29	iii	Papill. erosion	2/22/41	2	Intracerv. 3 cm.	7/ 2/41	Healed
55	34	ii	Small erosion	2/28/41	1	Flat to cervix	3/28/41	Healed
56	36	0	Small erosion	3/ 3/41	1	Intracerv. 6 cm.	3/24/41	Healed
			Endocervicitis					
57	31	i	Large erosion	3/22/41	1	Flat to cervix	6/15/41	Healed
58	20	0	Large erosion	5/24/41	1	Flat to cervix	6/17/41	Healed
59	36	iii	Large erosion	5/26/41	1	Endocerv. 6 cm.	6/30/41	Healed
			Endocervicitis	5/26/41	1	Flat to cervix		
60	50	iv	Small erosion	6/10/41	1	Intracerv. 6 cm.	7/10/41	Healed
			Endocervicitis					

lesions to heal was 63.4 days. Only two patients, belonging to the endocervicitis group did not improve, a failure of 3.3 per cent. Patients 18 and 25, who also belonged to the endocervicitis group, were already classified as failures, but when they returned at a later date, the examination revealed the cervical canal healed. As can be seen from Table I, a considerable time may elapse before the beneficial results become apparent. These observations convinced us that the final judgment for success or failure should be postponed until at least six months have elapsed from the first treatment given. Patient 13, diagnosed as large circular erosion and nonspecific endocervicitis, developed after a second treatment of eight minutes, 5 cm. intracervically, fever with pain in the lower abdomen, which subsided after four days. Three days later she was examined at the clinic. The vaginal examination failed to reveal any involvement of the parametria, but the cervical discharge was still as profuse as before. She did not return for further observation and had to be classified as failure. A similar reaction took place in Patients 16

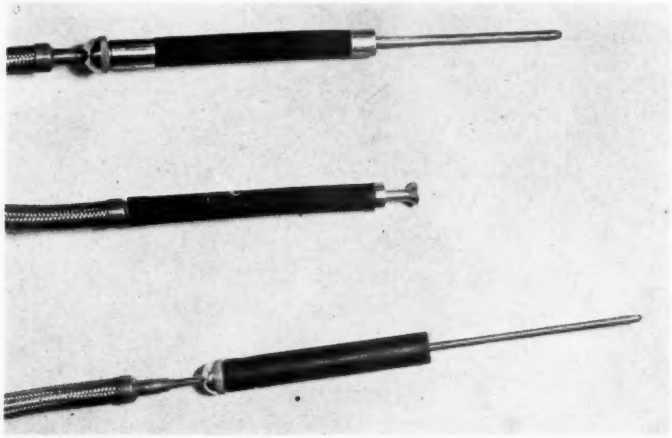

Fig. 2.—Applicators, showing portions of the flexible high pressure metal tubes leading to the distribution chamber.

and 17, in whom the applicator was inserted for more than 3 cm. into the cervical canal and the freezing applied for more than five minutes. Neither developed a cellulitis or a parametrial abscess, and in both patients the cervix cleared up in less than four months. The failure of Patient 10 to respond to the treatments may partly be ascribed to her refusal to have the malposition of her uterus rectified.

In cases of erosions of the cervix, the character of the lesion determines the length of the treatment. Plain superficial erosions may be treated for one to two minutes. Large circular erosions, including those of the papillary type, ectropions, and cervical polyps require from two to ten minutes' treatment. In patients with endocervicitis, where the applicator is introduced into the cervical canal for more than 3 cm., the treatment should not exceed two minutes. From our experience it seems advisable to treat erosions of the cervix not oftener than once every two weeks, and to repeat intracervical applications only once every four weeks. In acute infections of the uterus, the application of quick freezing, even for a very short period, is absolutely contraindicated.

SUMMARY

A new apparatus for quick freezing, the basic operating principle of which is the same as that of the electric refrigerator, has been described. The applicators are especially designed for gynecologic therapy and the apparatus is equipped with a defrosting device, which greatly simplifies their removal from frozen tissue.

Excellent therapeutic results were obtained with this instrument in 60 cases of chronic endocervicitis, cervical erosions and cervical polyps.

I wish to express my grateful appreciation to Dr. Ashley M. Brand for his helpful assistance in developing the quick-freezing therapy, and for supplying me with the data of his patients treated at the Chicago Maternity Center; also to Mr. R. W. Krieger for cooperation in constructing the apparatus.

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25 EAST WASHINGTON STREET

DeMarsh, Q. B., Alt, H. L., Windle, W. F., and Hillis, David S.: The Effect of Depriving the Infant of Its Placental Blood, J. A. M. A. **116:** 2568, 1941.

Deprivation of the infant of its placental blood by clamping the umbilical cord immediately after delivery results in significantly lower values for red blood corpuscles and hemoglobin during the first week of life than are encountered when clamping is delayed. In addition there is an increase in the number of reticulocytes in the blood. The placental blood belongs to the infant, and his failure to get this blood is equivalent to submitting him to a rather severe hemorrhage. Failure to receive this placental blood is especially important in prematures. It is estimated that 25 per cent of the infant's total blood volume may be lost by clamping the cord immediately after delivery. The authors condemn the practice of clamping the cord immediately after birth, and incidentally condemn the use of placental blood for transfusion purposes.

WILLIAM BERMAN.

LOCAL ARGYRIA OF UTERUS AND TUBE*

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ARGYRIA, local or general, results from absorption of silver compounds by a mucous membrane or by tissue fluid. The silver may be applied as a soluble salt, an organic compound, or in colloidal form.[10-12, 17] Metallic silver can be oxidized by body fluids. The resulting silver compounds, probably silver albuminates,[7, 9, 14] are absorbed. Rodin[15] described a case of argyria of the eyeball in a patient who carried a silver stylet in the lacrimal sac for seventeen years. Warthin[16] found extensive argyria of the inguinal lymph nodes twenty years after the insertion of silver wire for repair of an inguinal hernia.

The danger of argyria, neglected since the abolition of long-standing treatment with pills of silver nitrate, has been stressed again in recent years[5, 9] due to many cases of argyria following intense local or intravenous treatment with modern silver compounds. Quantitative investigations have proved that the human body may deposit a certain amount of silver in connective tissue before general argyria appears. In intravenous treatment with silver arsphenamine,[5, 8] the absorption can be estimated quantitatively. Under such conditions a definite relation between the total dosage and the silver content of the skin has been established.

The silver, once deposited, remains unchanged for a lifetime. Reports about the appearance of definite argyria after the application of silver for relatively short periods[1, 2] suggest that the patient has received some other silver medication during earlier periods of his life.

Only very few instances of argyria of the female genital tract have been described.[3, 6, 13] In some cases of general argyria the ovaries and the uterus were found to be affected. Local application of silver solutions to the cervix or cervical polyps[4] resulted in local discoloration, which was shown to be due to argyria. A study of available literature failed to disclose a report of argyria due to metallic silver slowly dissolving in the uterine cavity. No record was found of argyria of the Fallopian tube. Therefore the following observation seems worthy of being put on record.

P. S., a 58-year-old white female, entered the hospital on March 5, 1941, because of something protruding from the vagina and right lower quadrant discomfort. These symptoms were present for three months. Her menses had been regular every twenty-nine days, of four to five days' duration, moderate flow, no dysmenorrhea, and had ceased in 1933. There had been no bleeding up to one week before admission, when it appeared and continued until entrance into the hospital. It was this symptom that alarmed her and caused her to come for treatment. There was nothing of significance in her past history, except that twenty-seven years ago a cervical silver pessary had been inserted. She was a para iv, gravida iv, with no pathology during her pregnancies or deliveries.

*Aided by a grant of the Dazian Foundation for Medical Research.

Her temperature and pulse were normal; blood pressure was 160/100. Vaginal examination showed a large, edematous, pedunculated, mucous polyp protruding from the vaginal introitus; a relaxed pelvic floor; no palpable uterine or adnexal pathology. Rectal examination found no palpable or visible pathology. Speculum showed the atrophic cervix with the polyp protruding from it.

Physical examination revealed no other abnormalities. The skin showed no evidence of pigmentation.

Laboratory Findings.—Blood count, urinalysis, and blood chemistry determinations were normal. The complement fixation and flocculation tests for syphilis were negative. X-ray examination of the pelvis reported the presence of a metallic foreign body (pessary) within the lesser pelvic cavity, most likely within the uterus.

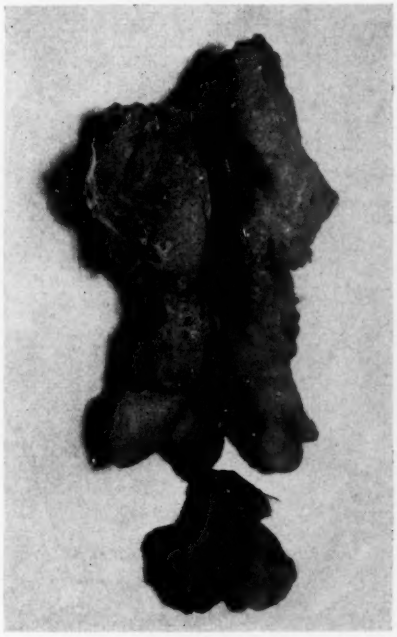

Fig. 1.

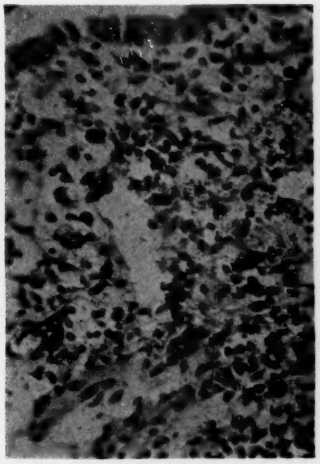

Fig. 2.

Fig. 1.—Uterus with pessary and cervical polyp.

Fig. 2.—Uterine endometrium showing the surface epithelium and the silver deposits in the stroma. ×150.

On March 8, 1941, a vaginal hysterectomy and perineorrhaphy were performed. The operative findings were several small intramural fibroids, a pedunculated cervical polyp, relaxed pelvic floor. When the uterus was opened, a Y-shaped pessary was found imbedded in the endometrium, and about 3 or 4 mm. above it a streak of dark material was seen in the cut myometrium.

Patient had an uneventful postoperative course and was discharged on March 20, 1941.

Examination of Specimen.—The specimen (Fig. 1) consisted of a uterus with cervix measuring 85 by 40 by 30 mm. The serosa showed no essential abnormalities. The myometrium was light brown in color; it measured up to 15 mm. in thickness. An intramural fibromyoma

measuring 15 mm. in diameter was present. The endometrial cavity measured about 40 by 20 mm. It contained a Y-shaped dark metallic foreign body (intrauterine pessary); the stem measured 18 mm., each of the two arms 19 mm. in length. One arm was deeply embedded in the left uterine horn. The endometrium measured up to 2 mm. in thickness; it showed a diffuse black discoloration. In the lower segment there was an ulcer measuring 18 by 4 mm. which was apparently produced by the stem of the pessary. The cervix showed a pedunculated polyp, measuring 11 by 7 by 4 mm. with many cysts filled with mucoid material on the section surface.

Microscopic Findings.—The surface of the endometrium was lined in some places by columnar epithelium, but in most places it was bare. In the stroma and in the superficial layers of the myometrium, there were present deposits of a brown and black granular material (Fig. 2). The granules were very fine and widely scattered. The surface and glandular epithelium was completely free of the deposits. Most of it

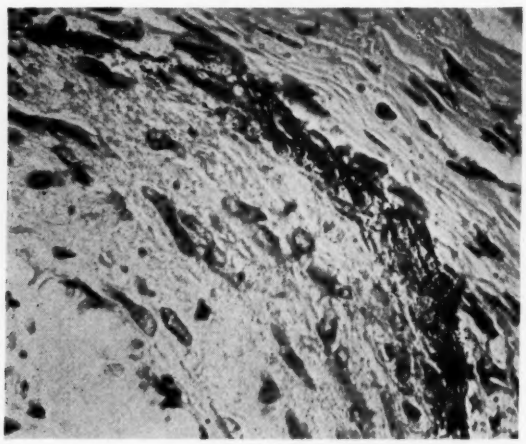

Fig. 3.—Wall of a blood vessel in the myometrium with massive deposits of silver granules in the adventitia. ×375.

was present in the connective tissue of the areas laid bare by the absence of the endometrial epithelium. It was found in the cytoplasm of the fibrocytes and in the intercellular fibers and spaces. Small amounts were seen in the endothelial cells lining lymph spaces. Some tissue spaces were dilated and filled out by cloudy light brown masses. High power magnification revealed them to be composed of very fine pigment granules. The coarser granules were brown or black in color. In some areas the material was seen in the connective tissue not in a granular form but forming fine threads resembling microscopic sections in which fibrils were stained with a silver stain. Smooth muscle cells in the myometrium were by far less intensely affected than the connective tissue cells. The pigment seen in the endothelial cells of small blood vessels was situated almost exclusively on the outer side of the nucleus away from the lumen. In the adventitial layer of the blood vessels the deposits were very dense, forming dark rings (Fig. 3). The epithelium and the connective tissue of the cervix were free from the granules.

In the intramural portion of the Fallopian tube the epithelium was free from deposits. The borderline between epithelium and connective

tissue was marked by an accumulation of granular pigment in the connective tissue cells (Fig. 4). The infiltration was less intense in the outer parts of the submucosa and still more dilute in the surrounding muscular tissue.

The appearance of this material, its localization, the lack of inflammatory reaction around the deposits suggested that it consisted of silver or a silver compound.

A portion of the pessary was examined chemically and found to give the characteristic reactions of silver.

Histologic sections of the uterus and tubes were stained with polychrome methylene blue and studied in the dark field.[8, 9] With this method a very much larger number of granules was visualized. The granules had a bright shine of yellow tinge which was described to be typical for silver particles.

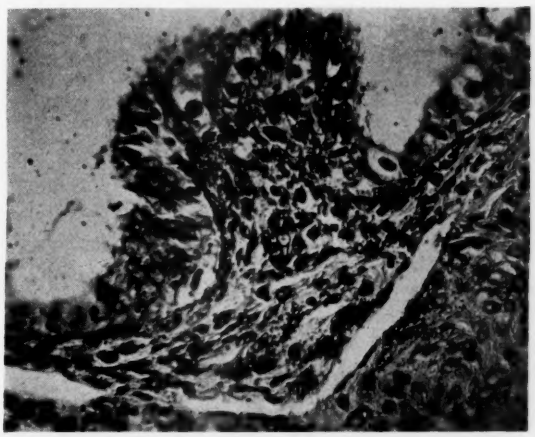

Fig. 4.—Section of Fallopian tube with deposits of silver granules in the subepithelial layers. ×265.

Seven per cent nitric acid did not dissolve the deposits, but application of 30 per cent nitric acid (for twenty minutes) dissolved some of the granules. When, after washing out the acid, ammonium sulfide was applied, some of the remaining granules turned dark olive brown in color (silver sulfide). Five per cent solution of sodium cyanide dissolved the granules in ten to thirty minutes. When the specimen was treated first with Lugol's solution of iodine and then with 2 per cent sodium cyanide, the partly dissolved granules reacted with the iodine turning yellow (silver iodide). Staining for iron pigment (potassium ferricyanide method) yielded a completely negative result.

These tests established the diagnosis of argyria of the uterus and the tubes. It has to be assumed that either the normal secretion of the uterine glands or the tissue-fluid oozing from the surface bare of its epithelium or both are capable of corroding silver if sufficient time elapses. The dark surface of the pessary proves that it was covered by an oxide. The material has been absorbed into the wall of the uterine cavity and into the wall of the tubes. In both it has been deposited mainly in the connective tissue, a characteristic finding of all forms of argyria.

Argyria of the uterus and tube is of relatively little clinical importance in itself. However, in the connective tissue of the cutis only a definite amount of silver can be stored, otherwise general argyria may appear. By any former application of silver the deposits may be close to this threshhold. Then the additional absorption of a relatively small amount of silver may lead to discoloration of the skin. In cases of otherwise unaccountable argyria in women, the possibility of absorption from a silver pessary should be kept in mind.

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MALIGNANT MESONEPHROMA OF THE OVARY

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THE term mesonephroma defines a group of ovarian tumors classified by Schiller[1] as having characteristic histologic features and said to arise from heterotopic rests of mesonephric tissue. In Schiller's original series of 10 cases, the age of the patients varied from 8 months to 69 years. Because of the findings and course in 7 of the 10 cases described, he believed that, clinically, the mesonephromas should be considered malignant tumors. Schiller also noted that only one of his cases appeared solely in the left ovary. This is in keeping with Popoff's[2] observation that embryologic defects in animals and man are more often found on the right side than on the left. Jones and Seegar[3] consider this evidence of the possible embryonic if not mesonephric origin of the tumor.

In the 6 cases reported by Jones and Seegar, the age of the patients varied from 41 to 72 years. Two of these tumors were malignant and 4 benign. In only one of these cases was the tumor solely in the left ovary. Jones and Seegar also pointed out that there were no symptoms by which these tumors could be clinically distinguished from other ovarian neoplasms.

Tuta and Siebel[4] recently added a case arising from the left ovary of a 49-year-old woman. In this instance the tumor was malignant.

REPORT OF A CASE

A 62-year-old white, married woman (S.B., Path. S.P. 41-1356) was admitted to the Jewish Hospital of Brooklyn on April 17, 1941, complaining of backache and constipation of many years' duration, loss of 10 pounds in weight within the past three months, and a bloody stool two weeks prior to hospitalization. Her last menstrual period occurred six years ago. Examination revealed a tense, movable, nontender cystic mass occupying the hypogastric region.

At operation a large cyst of the left ovary was found. The tumor was adherent to the sigmoid, rectum, uterus, and broad ligament. The contents of the cyst were aspirated before removal and thin, grayish fluid was obtained. Inside the cyst wall was a cauliflower-like growth

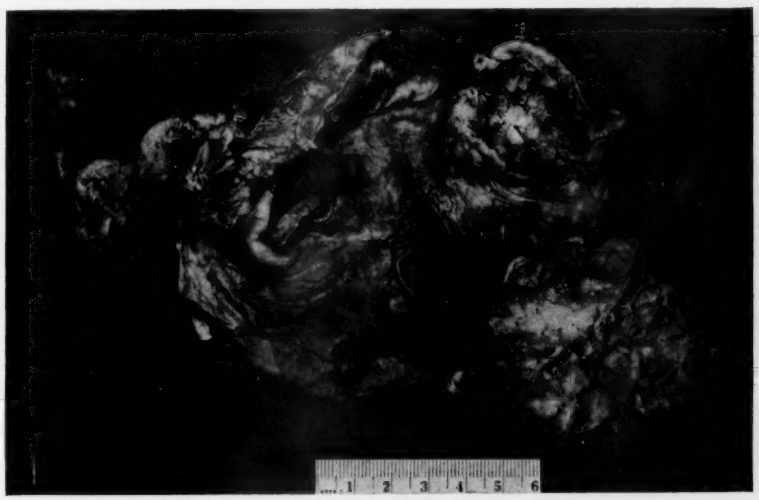

Fig. 1.—Tumor showing solid and cystic structure.

about 5 cm. in its greatest diameter. The right tube and ovary presented normal senile changes. The abdominal viscera were explored and no metastatic foci were found. A supracervical hysterectomy and bilateral salpingo-oophorectomy was performed after freeing the wall of the cyst from adhesions.

PATHOLOGIC REPORT

A. *Gross Description.*—The specimen was a pear-shaped uterus, amputated above the cervix, with attached Fallopian tubes and ovaries. The anterior surface of the uterus was smooth and glistening; the posterior surface was roughened. There was a soft endometrial polyp projecting into the uterine cavity. The myometrium contained several small leiomyomas. The Fallopian tubes and right ovary presented nothing of note. The left ovary was intimately adherent to the Fallopian tube. The ovary was represented by a cystic mass measuring 10 by 8 by 2.8 cm. The external surface was pink gray, smooth, and

glistening in some areas and roughened by fibrous tags in others. Projecting into the lumen and firmly adherent to the wall were several large, soft, polypoid and cauliflower-like gray, red and yellow nodules which measured up to 7 by 5 by 2 cm. The cut surfaces of these masses were

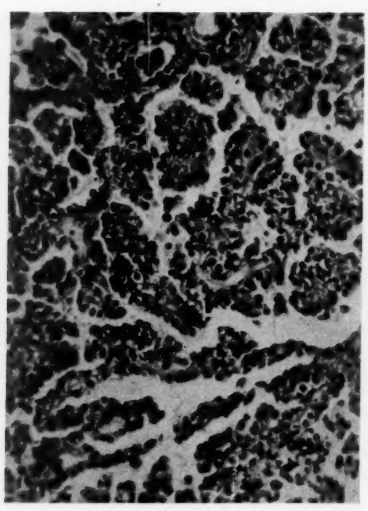

Fig. 2.

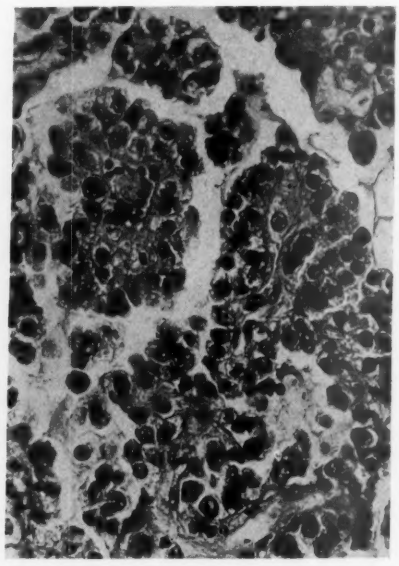

Fig. 3.

Fig. 2.—Section showing glomerularlike formations. (H. & E., ×250.)
Fig. 3.—Same as Fig. 2, ×525. Note capillary in glomerularlike tuft.

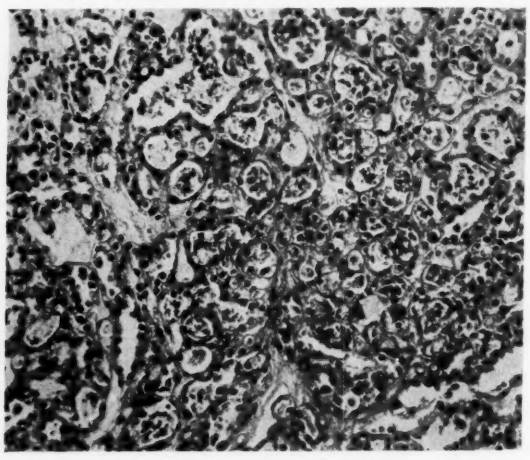

Fig. 4.—Section showing irregular lumina lined by cells with projecting nuclei. (H. & E., ×185.)

composed of opaque stalks of gray yellow translucent tissue. The remainder of the inner lining of the cyst was gray, smooth, and glistening and occasionally showed small papillary projections of yellow tissue similar to the large mass described above.

B. *Microscopic Description.*—Preparations from the uterus, right ovary, and Fallopian tubes were not remarkable. Preparations from the cystic and papillary portions of the tumor showed numerous papillary intracystic formations composed of irregular projections covered by low cuboidal cells or endothelial-like cells having sparse cytoplasm and projecting nuclei. In places small capillary loops were present within such papillary projections. Some of these structures closely resembled rudimentary glomeruli. There were also many scattered small and large irregular spaces lined by markedly flattened cells or by the endothelial-like cells with projecting nuclei and scanty cytoplasm. Some of these tubules contained homogeneous pink- and lavender-staining material. In the solid portions of the tumor many more irregular various-sized tubules were present, some of which were almost completely filled with

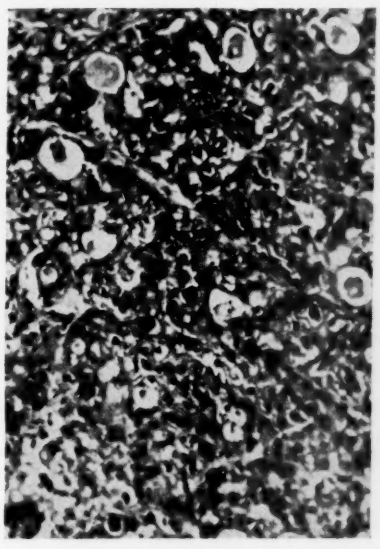

Fig. 5.

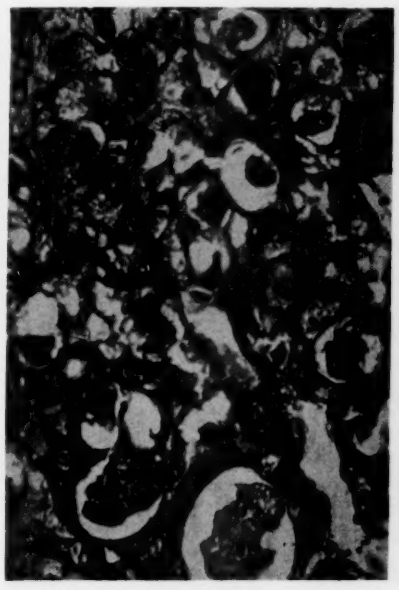

Fig. 6.

Fig. 5.—Section showing lack of differentiation, hyperchromatism, and giant cells. (H. & E., ×250.)

Fig. 6.—Same as Fig. 5, ×525.

pink- and lavender-staining material. In other areas, however, the cells appeared in small nests separated by broad bands of dense collagen. The cells showed marked variations in size and shape and contained deeply staining nuclei. Some were giant cells and contained more than one nucleus. Nucleoli were likewise prominent in some of these cells. There were also groups of large polygonal cells having foamy cytoplasm and relatively small vesicular nuclei. The cyst wall consisted of dense hyalinized fibrous connective tissue and was lined by low cuboidal cells.

COMMENT

This cystic neoplasm fulfills the criteria of mesonephroma ovarii as defined by Schiller and others. The tumor contains structural units resembling mesonephric glomeruli, and in some, well-defined capillary

loops were seen. In places, cells lining the cystic spaces contain sparse cytoplasm and buttonlike projecting nuclei common to the flat cells of the visceral layer of Bowman's capsule. Well-defined tubular structures are also seen. In addition, the histologic picture shows definite evidence of malignancy, which also is in keeping with most of the tumors of this type previously described in the literature.

While previous observation suggests that mesonephroma ovarii arises usually on the right side, it is well to note that in this instance, the tumor appeared solely in the left ovary. However, definite conclusions as to the side of predilection, if any, should not be drawn until many more cases have been reported.

With this case included, 12 of 18 patients were women aged 40 or over. This would seem to indicate that mesonephroma ovarii is a tumor usually occurring in the later years of life, but again too hasty conclusions should not be drawn until the series is larger.

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BILATERAL TUBAL PREGNANCY

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IT IS our purpose to add another instance of bilateral tubal pregnancy to the growing list of accepted cases in the literature.

Fishback[1] emphasized the importance of the correlation of the clinical data with the description of the fetuses, or parts thereof found, as well as the placental elements. He further gave a review of the literature, listing 75 acceptable cases to which he added one, bringing the total to 76 cases. Torpin[2] quoting Fishback's series added another case bringing the total to 77 cases. He emphasized the necessity of considering bilateral simultaneous tubal pregnancy as a form of double ovum twin pregnancy, similar to the so-called heterotopic pregnancy of which there are some 300 cases in the literature. Behney and Hanes[3] reported a case of bilateral tubal gestation in which they felt that the two pregnancies must have occurred within a comparatively short interval of time, though they might not have been viable simultaneously. The point of inspecting both adnexa at the time of operation for tubal pregnancy is brought out. Lee and Stone[4] reported a subsequent case, bringing the total number of cases in the readily available literature to 80. McIlrath[5] reported a case of bilateral tubal pregnancy which was not proved by microscopic examination.

CASE REPORT

A negro woman, 26 years of age, married, was admitted to the Roper Hospital on Feb. 25, 1941, at 12:04 A.M. with the complaint of "pain

in stomach." She had been well until about four hours prior to admission, at which time there was sudden onset of cramplike pain in the right lower abdominal quadrant just above the inguinal ligament. The patient vomited once. She did not faint but suddenly felt very weak. The pain remained cramplike and intermittent in quality but had subsided considerably in intensity by the time the patient was first seen by the house staff.

Review of the menstrual history revealed that the menses had begun at the age of 13 years, had been fairly regular at twenty-eight to thirty-day intervals, and with an average duration of four days. The patient had had two labors at term; both children were living and well, the youngest was two years of age. The last menstrual period had begun Feb. 5, 1941, lasting eight days. The preceding periods in January and December had been uneventful and had lasted four to five days each. On the day before admission she suddenly began to flow quite profusely; this had slackened by the time the patient was first seen. No history of dysuria or other symptoms referable to the genitourinary tract.

Physical examination revealed a drowsy young negro woman lying quietly in bed complaining of air hunger. The respirations were of sighing quality at times. The pulse was 120, rapid and thready. Respirations were 40 per minute. Blood pressure was 56/36. The skin was dry and cool to the touch, and there was slight rigidity of the abdomen, particularly over the right lower quadrant. Pelvic examination revealed a moderately relaxed perineum. Bartholin's and Skene's glands were not remarkable. The cervix was parous in type, softened in consistency and dark red in color. There was some bloody discharge from the external os. The uterus was in second degree retroversion and slightly enlarged. There was a questionable mass in the right fornix. Hemoglobin was 6 Gm.; white blood count, 18,000, with 83 per cent polymorphonuclear leucocytes.

The diagnosis of ruptured ectopic pregnancy was made, notwithstanding the lack of history of a missed period. The patient was given 500 c.c. of a 10 per cent glucose solution, followed by 500 c.c. of citrated blood during the course of the operation. Under ether anesthesia, the abdomen was opened through a lower midline incision. The peritoneal cavity was found to contain an estimated 2,000 c.c. of fluid and clotted blood. The right Fallopian tube was distended in its distal half to a diameter of about 4 cm. and blood was dripping from a small rent on the posterior aspect of the swollen portion. The left tube presented a nodular swelling in its midportion, about 2 cm. in diameter, and was of a dusky red color as seen through the serosa. The serosal surface of the right tube and cortical surface of the right ovary appeared smooth and regular; the corresponding surfaces of the left side showed a few old fibrous adhesions of delicate character. Both ovaries were of average size, as was also the body of the uterus. Both Fallopian tubes were removed and the abdomen closed without drainage. No corpus luteum was identified in either ovary at the time of operation.

The right Fallopian tube showed a prominent dilatation of the distal half, and measured 3.0 cm. in diameter. There were a blood clot on the serosal surface and a perforation on the posterior aspect of the tumefaction from which blood was oozing. Transverse section through the middle third revealed a centrally situated amniotic sac, measuring 1.5 cm. in diameter, containing a small embryo. This was surrounded

by a zone of hemorrhagic and gray tissue which appeared to have eroded the tubal wall posteriorly at the point of perforation.

The left Fallopian tube showed a nodular dilatation of its middle third, measuring 2.2 cm. in diameter. The fimbriated extremity was contracted and distorted by well-formed fibrous adhesions. Transverse section through the nodular swelling showed the lumen to be distended by a blood clot of lighter brown color than that seen in the case of the right tube. One segment of the circumference of the wall appeared eroded and paper thin.

Microscopic section of the dilated right Fallopian tube, which was seen grossly to be ruptured, showed the lumen to be occupied by fresh blood clot and a scattering of polymorphonuclear leucocytes, enmeshed in which were fairly numerous chorionic villi with two layered trophoblastic covering. Some few villi were necrotic. There was destructive infiltration of the musculature of the wall by chorionic villi and trophoblasts. Necrosis with loss of continuity of the muscle elements and

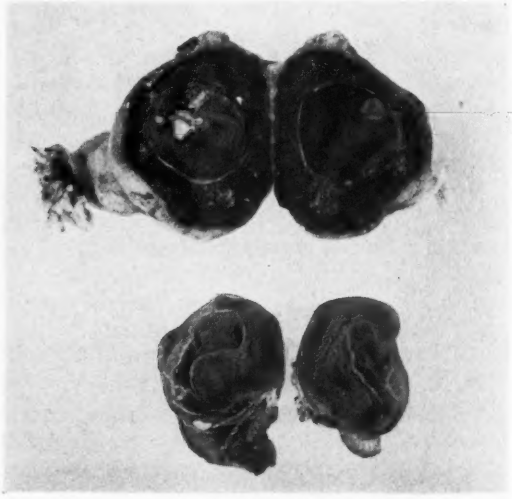

Fig. 1.—*Above:* Right tubal gestation, ruptured. *Below:* Left tubal gestation, regressing.

fibrous stroma and fresh hemorrhage on the serosa attested to complete perforation of the tubal wall. Adjacent to this rent, replacing necrotic musculature, was a fibrinoid zone. The muscle fibers of the wall showed hypertrophy and the intervening supportive stroma was edematous and infiltrated by round cells; there was early purulent exudation present about vessels. On the serosal surface an occasional disrupted fairly well-vascularized fibrous adhesion, partially covered by hyperplastic mesothelium, was noted.

Microscopic section of the left Fallopian tube showed the dilated lumen to be occupied by clot in which the silhouette forms of necrotic chorionic villi and some cell forms, judged to be trophoblasts, were discernible. The latter showed deep infiltration into the wall. Around the periphery was a fibrinoid layer and focal aggregates of xanthic macrophages containing blood pigment. In association with the latter were proliferating fibroblasts, evidence of early organization. In one zone the tubal wall was eroded and reduced to a very narrow confining zone

of muscle and fibrous tissue. Inflammatory round cells were scattered in foci throughout the wall and serosal adhesions were more pronounced than in the case of the foregoing tube. Incorporated in one section was the fimbriated extremity of the tube showing clubbing of the mucosal villi, fibrous tissue increase and inflammatory round cells in the stroma of the mucosa.

DISCUSSION

As seems to be the general rule in cases of bilateral tubal pregnancy, there was no indication from the history or physical findings in this case that such a condition existed, though the patient was evaluated as a relatively intelligent woman.

The question arises as to whether or not these two tubal pregnancies were viable simultaneously. The fact that the left tube was filled with older blood clot, contained necrotic chorionic villi, and showed blood pigment phagocytosis in its wall along with evidence of early organization of the clot would indicate regression, the age and duration of which are controversial. It is notable, however, that organization, as evidenced by fibroblastic activity, was very early, certainly not advanced. Such fibrous tissue increase in the tubal wall that existed appeared to be a part of the same inflammatory scarring reflected in the serosal adhesions found in the case of both tubes and mucosal stroma of the left. It further seems that with the marked degree of destruction and thinning out of the wall of the left tube that was present in association with trophoblastic penetration, reparative organization would certainly have been more conspicuous if sufficient time had elapsed. All factors considered, the evidence for simultaneous viability of these tubal pregnancies at one time appears presumptively strong. It is unfortunate that conditions at the time of operation did not allow for closer scrutiny of the ovaries for corpora lutea. It is considered significant that both tubes in this case showed old fibrous adhesions and the left showed the fibrous relic of endosalpingitis as well. This recalls the part played by inflammatory scarring, acting as a mechanical hindrance to the passage of the fertilized ovum, in the causation of tubal pregnancy.

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DESMOID TUMOR OF THE BACK

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SINCE desmoid tumors in some instances may resemble sarcomas, a desmoid fibroma of the back clinically suspected of being a metastasis from an anaplastic uterine sarcoma removed eleven and one-half years before, presents an interesting case for clinical and pathologic correlation.

The term "desmoid" was first applied by Johannes Müller in 1838 to designate a peculiar hard tendonlike tumor. The nature of a desmoid tumor is that of a benign fibroma arising from musculoaponeurotic structures, or the endomysium according to Ewing.[3] Some of the tumors classified as desmoids may be neurofibromas, according to Ewing[3] and Penick.[9] Desmoid tumors are most commonly found in the abdominal wall of women who have borne children, although they have been observed in nulliparous women, and rarely in the abdominal wall of men. Penick,[9] from an analysis of reviews covering over 500 desmoids, found 17 which occurred in postoperative scars. The postoperative cases predominated in females and usually occurred about one year after operation.

Desmoids are found much less frequently in locations other than the abdominal wall. Nichols,[7] in a series of 31 desmoid tumors at the Mayo Clinic from 1910 to 1922 inclusive, found 6 instances in muscles outside of the abdominal wall. Five cases were suspected of being sarcomas, the other was in a woman, 36 years of age, in whom a radical mastectomy had been performed for the removal of a tumor in the left lower inner quadrant of the breast. Mason[5] reported a series of 27 desmoid tumors at the Mayo Clinic during the years 1923 to 1929, inclusive. Nine of these tumors were located in relation to various muscles other than the abdominal group. Bellanger[1] reported a muscular fibroma, developing at the level of the scapular insertion of the serratus magnus muscle, and briefly reviewed several cases in the literature involving muscles other than abdominal.

CASE HISTORY

A widow, 51 years of age, entered the Grant Hospital on Jan. 11, 1928, complaining of lumbar pain of several years' duration. A diagnosis of a uterine fibromyoma had been made several months before. She had had 3 pregnancies and one miscarriage. The red cell count was 3,550,000. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed by Dr. E. W. Fischmann. A gross diagnosis of a soft degenerated uterine fibromyoma was made. There were polypoid masses which filled the uterine cavity.

Microscopic examination showed anaplastic sarcomatous areas in a fibromyoma with numerous large hyperchromatic tumor giant cells with multiple prominent nucleoli. There were areas resembling the ordinary

benign fibromyoma with cystic degeneration and hyalinization. There were also large hyperchromatic tumor cells embedded in dense connective tissue.

On Aug. 1, 1939, the patient entered the Grant Hospital for the removal of an egg-sized mass on the left side of her back. She first noticed the lump seven months before and at that time it was about the size of her thumb. She had occasional slight pain. The tumor mass was slightly movable and unattached to the skin. At operation it was found

Fig. 1.—Desmoid tumor showing interlacing bands of dense fibrous tissue and irregular softer areas containing muscle fibers.

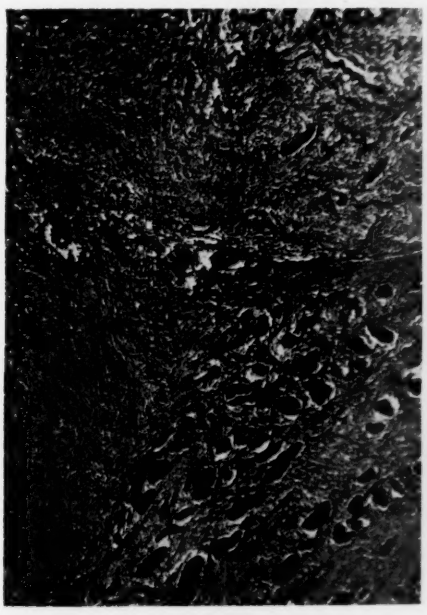

Fig. 2.

Fig. 3.

Fig. 2.—Showing moderately cellular connective tissue widely separating muscle fibers. Mallory's phosphotungstic acid hematoxylin stain. ×40.

Fig. 3.—A higher magnification showing the muscle fibers separated by desmoid tissue. Mallory's phosphotungstic acid hematoxylin stain. ×112.

to lie on the left side near the spinal column over the twelfth rib. A transverse incision was made through the superficial fascia and then through the aponeurosis of the latissimus dorsi muscle. The tumor mass was found to be intimately attached to the underlying sacrospinalis and posterior inferior serratus muscles. The surgical specimen was very hard and measured 6 by 5 by 4 cm. It was partially covered by muscle tissue. The surfaces made by sectioning showed interlacing bands of dense white tissue and irregular softer brown areas particularly at the periphery.

Microscopic examination showed a moderately cellular connective tissue through which were scattered isolated muscle fibers. With the Van Gieson, Masson trichrome and Perdrau silver stains, the arrangement of the connective tissue elements was clearly outlined. The connective tissue cells displayed no nuclear anaplasia. The Masson trichrome and Mallory's phosphotungstic acid hematoxylin stains showed the muscle fibers standing out in sharp contrast with the cross-striations of many of the muscle fibers showing distinctly. In some of the fibers there were degenerative changes and in others wide separation of the myofibrils.

DISCUSSION

The histologic examination of the tumor involving the back muscles revealed the structure to be a typical benign desmoid without relation to the uterine sarcoma removed previously. If the connective tissue had been very cellular in character, the question of a sarcoma might readily have arisen. Waugh[11] stated that recent unpublished studies by Pearman and Mayo indicated that the desmoid type of tumor is definitely benign. Recurrences are attributed to incomplete removal at operation. Marlow[4] reported a tumor in the trapezius muscle of a woman 26 years of age which was clinically a desmoid, but the very cellular character of the connective tissue suggested a sarcoma. There was no recurrence after eight years. Roentgen ray therapy was given because of the suspicion of a fibrosarcoma. Donald and Caylor[2] reported a desmoid tumor having cellular areas considered sarcomatous. Warren and Sommer,[10] in a study of fibrosarcomas of the soft parts, classified desmoid tumors as being histologically sarcomas. The peculiar localization of the majority of desmoid tumors in the musculoaponeurotic structures of the abdominal wall in women who have borne children suggests that trauma may be a predisposing factor and that a hematoma in the muscle may be the initiating factor.

The uterine sarcoma, in the case we are reporting, was thought to arise in a pre-existing fibromyoma and to be of myogenic origin. Ewing[3] and Novak[8] discussed the difficulties connected with determining whether a malignancy develops as a transformation of a pre-existing benign fibromyoma or whether it was malignant from the beginning. The large hyperchromatic tumor cells in the uterine sarcoma gave the impression of dealing with a very active malignant process, if we depend only on histologic structure as a criterion for malignancy. However, metastases are very rare in malignant uterine myomas, Ewing[3] having encountered only 3 such cases with generalized spread. According to Novak,[8] the type arising in uterine myomas is in general less malignant than from the endometrium or myometrium. McFarland[6] concluded that with malignant myomas metastases constituted the only proof of malignancy.

He also cited a case, referred by Dr. Jonathan Wainwright, of a patient who had a "suspicious fibroid" removed and in whom there later occurred metastases in the neck, thigh, and abdominal wall. The metastases were removed surgically and the patient was alive twelve years following the hysterectomy.

SUMMARY

A desmoid fibroma involving the sacrospinalis and posterior inferior serratus muscles of the back is reported. A supracervical hysterectomy was performed eleven and one-half years before with removal of an anaplastic uterine sarcoma. The patient is alive and well thirteen and one-half years following the hysterectomy, and there is no recurrence from the uterine sarcoma or the desmoid tumor of the back. Clinically the desmoid was suspected of being a late metastasis from the uterine tumor.

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GANGLIONEUROMA COMPLICATING PREGNANCY

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GANGLIONEUROMAS have been located in all parts of the body, but they are most prominent in the retroperitoneal spaces of the thorax and abdomen. In this report we are chiefly concerned with those tumors found in the abdomen and pelvis.

Beneke reported the first case of pelvic retroperitoneal ganglioneuroma in 1898; only 13 have been reported up to 1940 according to Turunen. Pick and Bielschowsky in 1911 revealed the true relationship between ganglioneuromas and the sympathetic nerve elements, and classified true neuromas on an embryonic basis. They named them embryonic sympathetic gangliomas. These tumors are now considered to develop at the site of cell nests that have become displaced during embryonic life and therefore are congenital in origin. They are seldom diagnosed before operation, and at times after operation they are diagnosed as fibromas, liposarcomas, or fibrosarcomas.

According to Evans and Francona, the tumor is more frequent in women than in men and more in the left side of the body than the right side. It is more prominent in the first twenty years of life. The

majority of these tumors are benign and cause symptoms because of pressure on the surrounding vital structures. These tumors are very slow growing and have been known to have been present for years with no tendency to become malignant.

Technical difficulties are usually encountered in the delivery of the tumor, since it tends to be firmly adherent to the adjacent structures. Of the 13 cases reported (Turunen), 8 patients were operated upon and 5 tumors were discovered at post mortem.

CASE REPORT

M. B., aged 20 years, white, unmarried, was admitted to the Booth Memorial (Salvation Army) Hospital in June, 1940. Her past history showed that her health had generally been good. She was nervous and had had indigestion for the past four or five years. She had the usual childhood diseases and had had no operations. She was seen some time ago by a physician who told her that she had a tumor of the ovary, and he advised operation. Family history was essentially negative. Her menstrual periods, which began at 15 years of age, occurring every thirty days, were regular, of moderate flow, and there was no dysmenorrhea. The last menstrual period was Jan. 6, 1940.

Her general physical examination was essentially negative. Pelvic examination showed a nulliparous vagina, with no evidence of infection. The pelvis was filled with a hard lobular mass rather fixed to the sacrum, about the size of a large grapefruit, which did not seem to be connected to the uterus. The uterus was enlarged to about a five or six months' gestation. The cervix was pulled up under the symphysis. X-ray of the abdomen showed the fetus outlined rather high in the abdomen, but no definite outline of a tumor mass could be made out. Pelvic measurements were within normal limits. Laboratory findings showed a negative Kahn test. The red blood count was 4,100,000 and the white blood count was 7,900.

Preoperative diagnosis was: a pregnancy of twenty weeks' duration, and dermoid cyst filling the pelvis.

At operation a large retroperitoneal mass was found filling the pelvis. It was fixed to the sacrum and to the iliac vessels and nerves. It was impossible to ligate the entire wide pedicle in one piece, and since the tumor seemed to involve the iliac vessels, most of it was removed, leaving a thin shell of tumor attached to the sacrum.

The specimen was examined by Dr. Sam Katz of the Booth Memorial Hospital Pathological Department.

The specimen consisted of a lobulated tumor, pale yellow, firm, and cutting like gristle. The tumor resembled a lipoma except for the firmness. On microscopic section, the connective tissue of the tumor was interposed with numerous cellular structures. Under special stain the larger and smaller groups of large round ganglion cells were seen. In general the ganglion cells had only one nucleus. Occasionally one found a double nucleus. The ganglion cells were well developed, sympathetic ganglion cells.

Postoperative diagnosis was a twenty weeks' gestation, and presacral ganglioneuroma.

The postoperative course was smooth and the pregnancy continued uninterrupted. Rectal examination on Aug. 13, 1940, showed a right posterior pelvic mass somewhat irregular and fixed to the pelvic wall,

which seemed to obstruct the inlet. The patient was permitted to go to term at which time a cesarean section was considered.

The patient began having contractions on Sept. 17, 1940. On examination it was felt that the pelvic mass previously palpated would not cause enough dystocia to obstruct labor. Labor was permitted to progress and she was delivered of a 6 pound 9 ounce female infant by means of perineal forceps over a right mediolateral episiotomy. No unusual difficulty was encountered in the delivery.

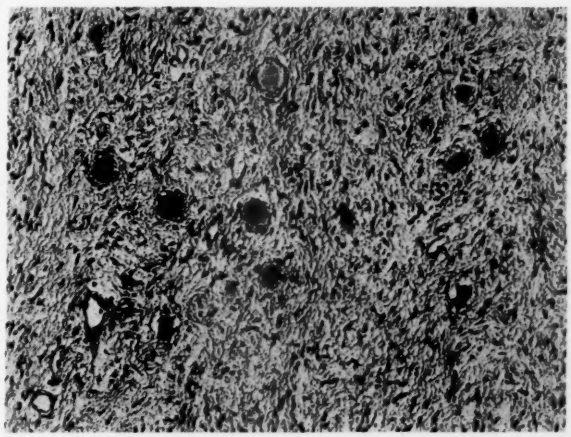

Fig. 1.—Section from tumor showing typical ganglion cells. Low power (×145).

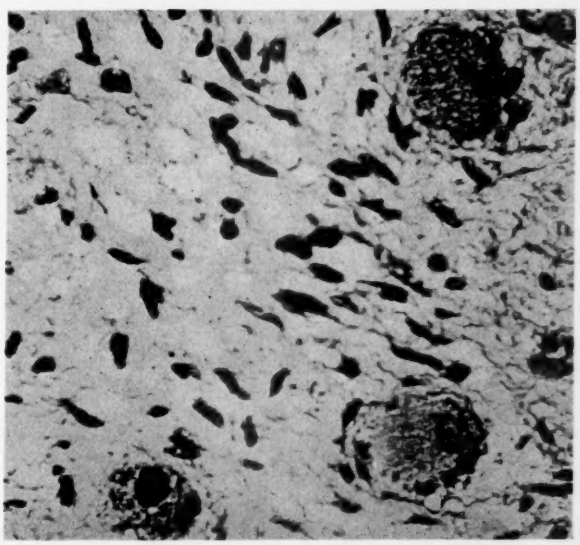

Fig. 2.—High power of section from tumor (×630).

The post-partum course was uneventful. On Sept. 22, 1940, a rectal examination revealed the mass to be smaller. Some induration could be felt on the right side. The patient was last seen Nov. 1, 1940, at which time the pelvis was normal and there was no evidence of any mass present. She had no symptoms referable to her pelvis.

COMMENT

This presents an unusual and interesting case. Very few cases of this tumor have been reported in the literature, but as mentioned before, it is probable that many have not been diagnosed and have found their way under the classification of other tumors such as fibromas, lipomas, liposarcomas, and fibrosarcomas. Because of the rarity of the condition a correct preoperative diagnosis is difficult, and the more common conditions are usually considered. The most interesting feature of the case was the complete disappearance of the remnants of the tumor after the patient had delivered. When the patient was last examined, she presented a normal pelvis.

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MONOAMNIOTIC TWIN PREGNANCY

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THE following case seems of interest because twins so rarely develop in one amniotic sac.

A white primipara, aged 27 years, entered the private service of Dr. Frank W. Lynch in the University of California Hospital on Dec. 1, 1940, in premature labor. Her expected date of confinement was Feb. 15, 1941; her last menstrual period May 8, 1940. The prenatal course had been uneventful. The Wassermann test was negative and the pelvis was normal. Twins had been suspected in the early months of pregnancy because of the relatively large size of the uterus, but the rate of growth then slowed down and the possibility was discarded. The family history revealed that the patient's maternal great aunt had twins but no other twins occurred in either the patient's or her husband's family.

On entering the Hospital, the patient stated that she had not felt any fetal movements for several days and that, four hours prior to entry, fleeting uterine contractions had begun, associated with suprapubic pain. These contractions had increased steadily in severity and at the time of examination were severe and occurred every one and one-half to two minutes. An excessive bloody show occurred as the patient entered the Hospital.

Physical examination disclosed: a uterus two fingerbreadths above the umbilicus; no fetal heart could be heard. The uterus was not unusually hard or tender between contractions. On rectal examination, the cervix was dilated 4 cm. with the membranes intact and a footling presentation.

Temperature, blood pressure, pulse, and respiration were normal. The hemoglobin was 83 per cent (12 Gm.). The blood type was IV (Moss).

The patient was given nitrous oxide and oxygen with her pains, and because vaginal bleeding persisted, a vaginal examination was made which showed a cervix completely dilated with membranes bulging through the os. These were ruptured artificially, when the lower edge of the placenta could be felt at the left posterior margin of the dilated cervix. Because vaginal bleeding still persisted, the feet were brought down rapidly and the fetus readily delivered as a breech presentation; the second, and much smaller, fetus, was expressed by pressure on the fundus. The first infant was a macerated premature fetus and weighed 1,300 Gm. The second infant was flat, almost papyraceus. It weighed

Fig. 1.

but 185 Gm. and measured 16½ cm. from crown to rump. Considerable bleeding occurred, both immediately after the delivery of the infants and of the placenta, the total blood loss being estimated at 1,200 c.c. Consequently, intravenous (10 per cent) glucose was administered to the patient immediately after the second stage, 1,000 c.c. in each antecubital vein followed shortly by a transfusion of 750 c.c. of citrated blood. The patient's condition was good throughout with no evidence of shock.

The placenta measured 22 by 16 by 2 cm. in size and weighed 720 Gm. The membranes were intact, but there was only one amnion and one chorion. No evidence of a partition between the two cords could be found, and, in addition, blood vessels from the larger of the two cords passed over the insertion of the smaller cord, entering the placenta in this area. The cords were inserted marginally, the one to the fetus papyraceus being 55 cm. long and but 0.5 cm. in diameter. The cord

to the larger fetus was 48 cm. in length and 1.5 cm. in diameter. At a distance of 30 cm. from the placenta, the two cords formed a complex true knot, while a separate true knot was present in the narrow cord in the same area. It seemed probable that the smaller fetus had died early in the pregnancy, possibly from a knot in its cord; and later had become entangled in the cord of the larger fetus, causing its death a day or two before the onset of the premature labor. The heart of the small fetus was grossly normal.

The patient's post-partum course was uneventful except for a rise in temperature to 38° C. on the third to sixth post-partum days, inclusive. Sulfanilamide was started on the fourth post-partum day, and coincided with a fall in temperature to normal within the next thirty-six hours. Blood counts on the first, fifth, and eighth post-partum days revealed the hemoglobin always above 80 per cent, and a maximum white blood count of 15,000. Urinalyses on the same days were within normal limits. The patient was up and in good condition on her tenth post-partum day.

DISCUSSION

A comprehensive review of the cases on monoamniotic twins was made by Quigley[1] in 1935. He stressed the rarity of the condition and states that from the time of the first case reports in the seventeenth century to 1935 he was able to find but 108 authentic cases to which he added one of his own. From the practical standpoint, the chief clinical interest is the danger of death of one or both fetuses from twisting or knotting the cords. This results in a high fetal mortality rate, but there is no more risk to the mother than in any other case of twin delivery. Quigley states that in 94 cases where it was possible to estimate mortality, the fetal death rate was 68 per cent. True knot formation was reported 58 times in the 109 cases, an incidence of 53 per cent. Eight monsters occurred in the series. Both twins survived in only 17 of the cases, a 15 per cent chance. (Since 1935, an additional case of survival of both infants has been reported by Parks.[2])

Quigley, in stressing the rarity of this type of twins, states that he was able to find only eight cases reported in the American literature from 1835 to 1935. In reviewing the case reports in the American literature, we find this group is even smaller, since one of the cases included in Quigley's study (Boyd,[3] 1883) is, in reality, a fetus papyraceus in a separate amnion. In fact, in describing the placenta of his specimen, Boyd states that "the fetal side shows the division in the amniotic sacs." In the six years since Quigley's study, we have found reports on three additional cases in the American and one in the British literature.[2, 4-6]

Taken with the case report above, five cases in the past six years would indicate that the extreme rarity of monoamniotic twins is due, in part, to a failure in reporting or recognizing the condition after the delivery.

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PENETRATING CHORIONEPITHELIOMA WITH RUPTURE OF UTERUS AND FATAL INTRA-ABDOMINAL HEMORRHAGE

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THE literature on chorionepithelioma includes numerous examples of the bizarre course this interesting tumor may take. Devastating growth rapidity may be contrasted with instances of spontaneous disappearance of a tumor which is, microscopically, highly anaplastic. This is a report of a classic hydatid-mole-chorionepithelioma sequence with extensive penetration of the uterine wall, spontaneous rupture into the peritoneal cavity, and fatal hemorrhage.

The *Quarterly Cumulative Medical Index* for the preceding twenty years reveals several titles of questionably similar cases, but in each instance the report appeared in an obscure and inaccessible foreign publication. More instances of this sort have undoubtedly been observed but not reported.

CASE REPORT

Y. O., a 24-year-old Japanese female (Hospital No. 754817), entered the Los Angeles County General Hospital on March 9, 1941. With the aid of an interpreter, the following history was elicited:

The patient asserted that she had never been pregant, but she passed a hydatid mole eight months before, in July, 1940. Subsequently, frequent irregular spotting and passage of clots occurred. On March 3, 1941, a week before entry, she was studied in another Los Angeles hospital because of an increase in the amount of spotting and frequent lower abdominal cramps; a positive urine Friedman test, radiologically negative lungs, moderately enlarged heart, and normal blood and urine were reported from this other hospital.

The patient was not acutely ill, and in good general physical condition. Blood pressure was 112/68. Bimanual pelvic examination showed the corpus uteri symmetrically enlarged to the size of a three to four months' pregnancy with a soft closed cervix and normal adnexal zones, with no masses. The red cell count was 3.8 million, hemoglobin 72 per cent, and leucocyte count 8,200, with a normal differential smear and a sedimentation rate of 26 mm. per hour. Urine examination was negative. A tentative diagnosis of threatened abortion was made, and she was placed on routine conservative therapy.

On March 12, 1941, at 12:40 P.M., three days after admission, the patient suddenly went into shock, the pulse became weak and flickering, and the blood pressure dropped to 60/0. The resident and I had made hospital rounds an hour before, and the patient seemed quite well at the time. The red cell count was 2.4 million, hemoglobin 32 per cent, and leucocyte count 6,400. Careful bimanual pelvic examination showed generalized abdominal tenderness; the uterus was only indefinitely palpable, the posterior vaginal fornix was soft, doughy, and seemed to bulge slightly. Shock therapy was administered immediately, including warm blankets, deep Trendelenburg position, and intravenous fluids.

The staff members concurred in a diagnosis of massive intra-abdominal hemorrhage, possibly due to rupture of the uterus.

Laparotomy was immediately performed, using field block procaine anesthesia with continuous oxygen inhalation. After incising the peritoneum, the abdominal cavity was found to be full of blood clots and liquid blood. A large mass of friable tumor tissue lay free in the cul-de-sac. There was a 4 by 2 cm. rent in the right superior aspect of the anterior wall of the uterus, with moderate bleeding issuing from the uterine cavity. A bluish nodule, 3 by 5 cm., occupied the anterior uterine wall near the cervix. On palpation, the entire uterus seemed very friable, the anterior wall and fundus were paper thin and mushy, and it was evident that hemorrhage could be controlled only by hysterectomy. The broad ligaments and adnexal attachments were rapidly

Fig. 1.—Specimen showing rupture of uterus due to penetrating chorionepithelioma.

clamped and divided, and because the cervix could be readily retracted upward, a cuff of vagina was incised around it and a rather easy total hysterectomy was performed. The vaginal opening was rapidly sutured, the adnexal stumps were joined and attached, and the abdomen was speedily closed. The patient was almost moribund upon arrival in the operating room, and despite a midoperative 500 c.c. citrated blood transfusion, continuous oxygen inhalation, and stimulants, she died during the course of the operation.

The pathologist reported: (1) Choriocarcinoma with perforation of the uterus; (2) decidual reaction in the endometrium; (3) hyperplasia of the myometrium typical of pregnancy; (4) theca lutein cysts.

Inability to communicate with the patient's family precluded permission for autopsy.

SUMMARY

A chorionepithelioma penetrated the uterine wall and resulted in spontaneous uterine rupture, extrusion of a free mass of tumor tissue into the peritoneal cavity, and fatal intra-abdominal hemorrhage.

THE "FROG" TEST (XENOPUS LAEVIS) AS A RAPID DIAGNOSTIC TEST FOR PREGNANCY*

PRELIMINARY REPORT

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DURING the past decade, two biologic tests for the determination of early pregnancy have come into general use, the Aschheim-Zondek (mouse) test and its Friedman modification (rabbit). The degree of accuracy of both of these tests is excellent, approximately 98 to 99 per cent, but the time element of ninety-six and thirty-six hours, respectively, is a drawback when speed is required in an emergency diagnosis of pregnancy.

In 1934 another biologic test, using the South African clawed frog, *Xenopus laevis,* was suggested.[1] Many different groups of investigators abroad have reported over 3,000 tests with 98 to 100 per cent accuracy in the use of this frog.[2] With this test for pregnancy, the time factor is greatly lessened (i.e., four to eighteen hours). The advantages of the frog test are obvious if the same accuracy and speed could be attained in America under different environmental conditions. We herewith report, for the first time in American literature, our findings with the frog test in 53 clinical cases of suspected pregnancy.

The "frog" test is based on the peculiar biologic function of the mature female *Xenopus* in that she carries eggs throughout the year, only extruding them with mating or after the injection of hormones peculiar to pregnancy. Since the test animals are kept isolated from the males, the extrusion of any ova following the injection of suspected urine becomes definitive for pregnancy (excessive gonadotropic hormone).

Apart from numerous experimental tests on known urines and various hormonal extracts[3] 53 separate unknown urines were tested on the frogs. Parallel tests were performed on segregated rabbits using the same specimens of urine. The urines were from women who had either missed one menstrual period or had not missed any menses but suspected the possibility of conception. None of the patients could be clinically diagnosed as either pregnant or nonpregnant by physical examination.

The results of the tests are shown in Table I. It will be noted that out of 53 cases, 51 showed rabbit and frog in agreement, and two showed

*Supplies of frogs at present are limited considerably by present war conditions. A detailed review of all the work on *Xenopus laevis* is in course of preparation.

TABLE I. COMPARISON OF FROG AND RABBIT TESTS

NO. OF TESTS*	XENOPUS (FROG) TEST	FRIEDMAN TEST (RABBIT)
18	18 negative	18 negative
33	33 positive	33 positive
1	+	-
1	+	-

*An additional case showed a discrepancy (i.e., frog negative and rabbit positive). However, since further specimens of this patient's urine were unobtainable, the disparity could not be checked and, therefore, this case cannot be included in the report.

discrepancy. In the first disagreement the frog indicated pregnancy and the rabbit nonpregnancy. However, owing to the history and clinical findings, this patient was operated upon soon afterward with a preoperative diagnosis of ectopic pregnancy. Upon laparotomy, an unruptured tubal pregnancy was discovered in the pelvis, the diagnosis of which was later confirmed in the pathologic laboratory. In this instance, the frog was proved to be correct and the rabbit false.

The second disagreement also showed the frog reacting positively and the rabbit negatively. In this case, both tests were repeated one week later using a second urine specimen. This time both animals were positive. Again, this would seem to indicate that the frog was more sensitive than the rabbit in diagnosing early pregnancy.

It is thus evident from our short series of cases that the frog is a very sensitive indicator of early pregnancy. While we do not suggest any necessity for replacing the Friedman test or the Aschheim-Zondek test in the usual pregnancy diagnosis, there would appear to be a distinct advantage in using the *Xenopus* test in very early or ectopic pregnancies, or where rapid diagnosis is desirable.

TABLE II. ADVANTAGES OF "FROG TEST"

		XENOPUS	A-Z (MICE)	FRIEDMAN (RABBIT)
1	Rapidity	4-18 hr.	96 hr.	36-48 hr.
2	Simplicity	No operation	Requires operation	Requires operation
3	Economy	16 cents per frog	5 mice cost a dollar	One rabbit, $1.50
4	Maintenance	Simple	Feeding and cleaning problem	Space occupying
5	Technique	Single injection	40 injections	One or two injections
6	Ease of injection	Subcutaneous	Multiple injections	Intravenous
7	Practicability	Can be used over and over again	Animals killed	Rabbit usually killed
8	Special precautions	None	Age and weight	Isolation
9	End reaction	Simple observation of eggs in water	Search for ovaries in five animals	Search for ovaries

TECHNIQUE

Frog Maintenance.—Our basic method of keeping the frogs entails the use of two 12-gallon aquaria for each ten frogs. One tank is used as a "rest" tank in which the animals recuperate for four weeks after receiving an injection, and the other tank is the "active" tank from

which animals ready for use are taken. The water in the tanks is kept at about a three inch level from the bottom. The frogs are fed small strips of beef heart, liver, and garden worms (if available) twice each week. Tank water should be changed to fresh water of the same temperature if the tank develops an odor.

For the actual tests, standard two-gallon tanks are used. These may be stacked one above the other for convenience in making a number of tests simultaneously. Half-inch wire mesh should be bent to form a platform about one inch from the bottom of each test tank to prevent the frog from devouring its extruded eggs. A set-up "test" tank should contain about three inches of water and should be kept covered with a glass plate, allowing for the passage of air. The water in all the tanks should be of the same temperature and the room for housing and testing should be bright and airy with little variation in temperature.

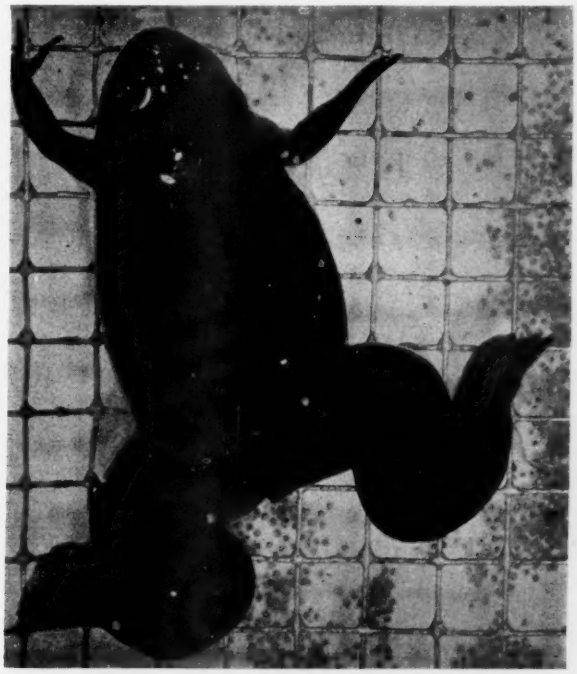

Fig. 1.—A positive reaction, showing hundreds of extruded eggs.

After each test it is advisable to burn off any contaminating eggs from the wire platform with a Bunsen burner, since occasionally some eggs adhere to the wire and may conflict with the results in the following test.

Concentration of Urine.—Although whole urine may be used, Crew and others suggest a simple concentration which can be performed in half an hour or less and which favors the more rapid deposition of eggs. The technique which we used follows: Eighty cubic centimeters of morning urine is acidified with glacial acetic acid until acid to litmus. Then 160 c.c. of acetone is added to the urine, causing a precipitation of proteins and hormones from the urine. The contents are thoroughly mixed and allowed to stand for fifteen minutes and then centrifuged. The supernatant fluid is discarded and the precipitate washed twice with 20 c.c. of ether. The precipitate is allowed to dry. Two cubic centi-

meters of distilled water are added to the dry precipitate and thoroughly stirred and then poured into a small centrifuge tube. Centrifuging again brings down excess protein while the hormone is soluble in the 2 c.c. of water. Just prior to injection the clear supernatant fluid is decanted and adjusted with 10 per cent sulfosalicylic acid to a pH of 5.5 by means of nitrazine paper (Squibb). One cubic centimeter of the concentrate is used for the injection while the remaining cubic centi-

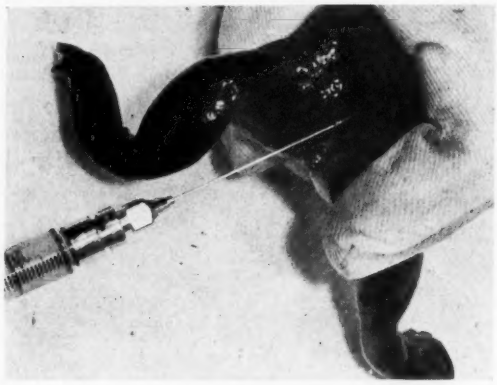

Fig. 2.—Injecting the *Xenopus*.

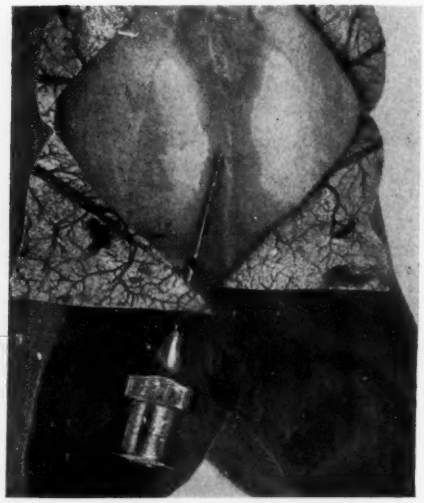

Fig. 3.—Dissection showing position of needle during injection.

meter is reserved for use in case of recheck, or a second frog may be injected immediately. By means of this simple concentration each cubic centimeter of the final concentrate is equivalent to 40 c.c. of whole urine.

Method of Injection.—Care as well as experience is required when injecting into the lymph sac of the toad. To miss the lymph sac and puncture the lung usually means death of the frog. The animal is injected by means of a long, flexible needle into the dorsal lymph sac. This lymph sac is reached by thrusting the needle superficially into the left thigh muscle, and then directing the point of the needle steadily

upwards to the middorsal line (Fig. 2). Throughout its course, the needle should be seen clearly just beneath the skin. A firm gentle thrust carries it through connective tissue into the lymph sac. Great care must be exercised to keep the point of the needle extending upward and away from the animal to avoid puncturing the left lung (Fig. 3).

Reading the Test.—After the animal has been injected with the urine concentrate, it is placed in the waiting test tank and watched. Positive extrusion of eggs may be seen as early as four hours after injection. The tests were read at eight to twelve hours, when reactions were usually complete. If after eighteen hours no eggs are visible in the tank, the test may be considered negative and the animal placed in the "rest" tank for use again in a few weeks.

Advantages of the Xenopus.—As will be noted from Table II the frog is at least as accurate as the rabbit. The test is simpler, more rapid, and more economical since the frogs can be used over and over again. The frogs are easier to handle, care for, and maintain than either mice or rabbits. The frogs require small amounts of foods and few feedings, the space and care are minimal, and the test requires only one subcutaneous injection of 1 c.c. of urine concentrate.

Other Hormone Reactions.—It has been demonstrated experimentally[4] that progesterone, testosterone, and adrenal cortical extracts in large doses will cause ovulation in *Xenopus laevis,* but since these hormones do not occur in normal urines in quantities sufficient to produce the reaction, the idea of conflicting results may be dismissed. However, the potential value of the frog as a biologic assay animal for anterior pituitary-like hormones should not be overlooked.

SUMMARY

A series of 53 suspected cases of early pregnancy tested with *Xenopus laevis* ("frog" test) and checked with the Friedman (rabbit) test showed 100 per cent accuracy in the frog. It is suggested that the "frog" test, because of its high degree of accuracy and the rapidity of reaction, four to eighteen hours, may be used where speedy pregnancy diagnosis is imperative. Other advantages of the frog test are discussed.

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ACCESSORY APPARATUS TO ASSIST IN PROPER POSTURING OF THE PELVIC INLET

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PELVIORADIOGRAPHY as advocated by Caldwell and Moloy requires, first, a set of stereoradiographs of the pelvic inlet with the patient in the supine posture. Proper posturing of the patient when taking stereoradiographs of the pelvic inlet is essential for later interpretation and typing of the pelvis.

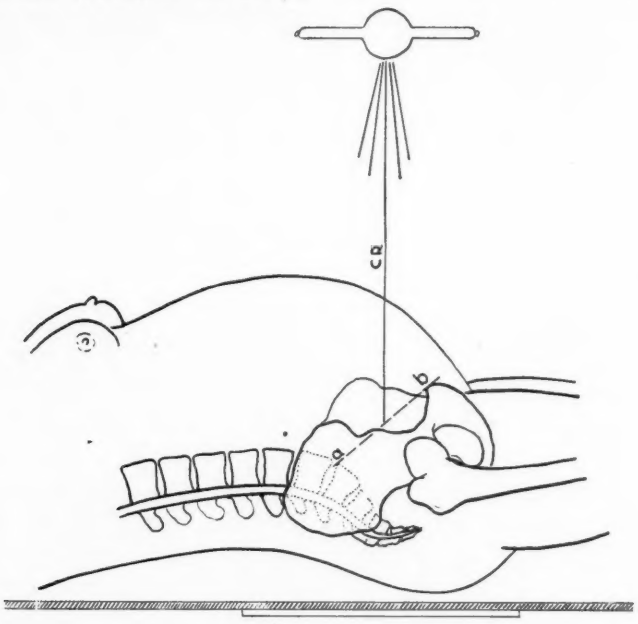

Fig. 1.—Plane of inlet *a-b* without pad.

It may be observed from Fig. 1 that with the patient in the supine position the plane of the pelvic inlet is not parallel to the plane of the film. In order that the pelvis may be typed with a minimum of difficulty, some device is necessary for tilting the plane of the inlet to bring it parallel to the plane of the film.

Caldwell and Moloy advocated the use of a lumbosacral pad as illustrated in Fig. 2, to place the pelvic inlet in its proper relation to the plane of the film.

This means of tilting the inlet has been practiced in the Department of Roentgenology of the Margaret Hague Maternity Hospital for some time. During this time I had occasion to notice a great deal of discomfort to the patient when the heavy pad was placed under the curve of the lower spine.

With a view to eliminating this discomfort and at the same time maintaining my standard technique, I had built an angle block with a 20 degree caudal slope. The patient rests supine on this block with a pillow underneath the head and shoulders without discomfort. The block must be so placed so the lower border of the block is pressing lightly against the superior margin of the patient's buttocks. Speed in handling our

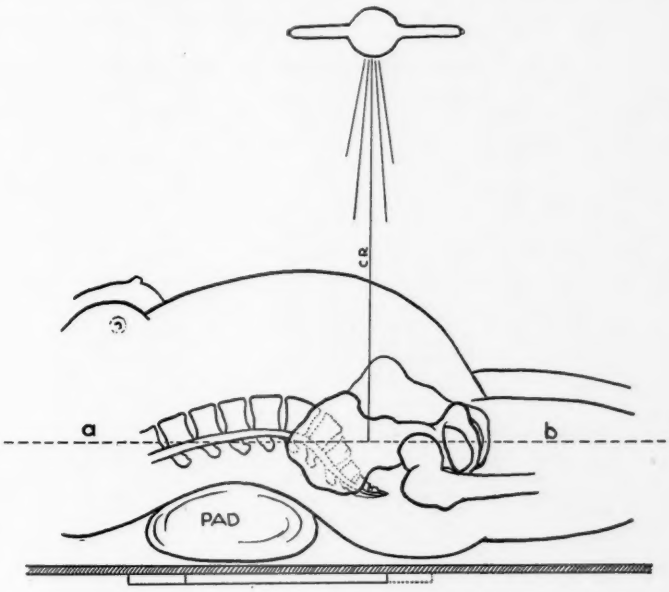

Fig. 2.—Plane of inlet *a-b* with pad.

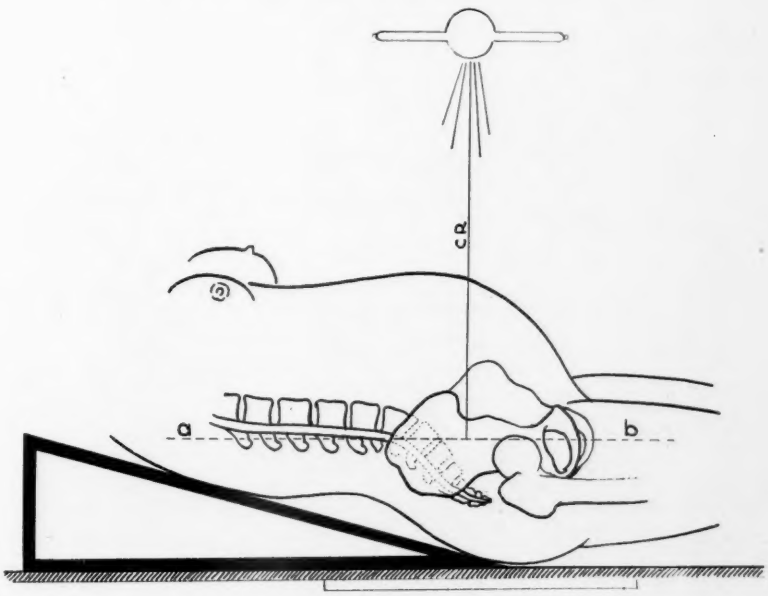

Fig. 3.—Plane of inlet with angle block *a-b*.

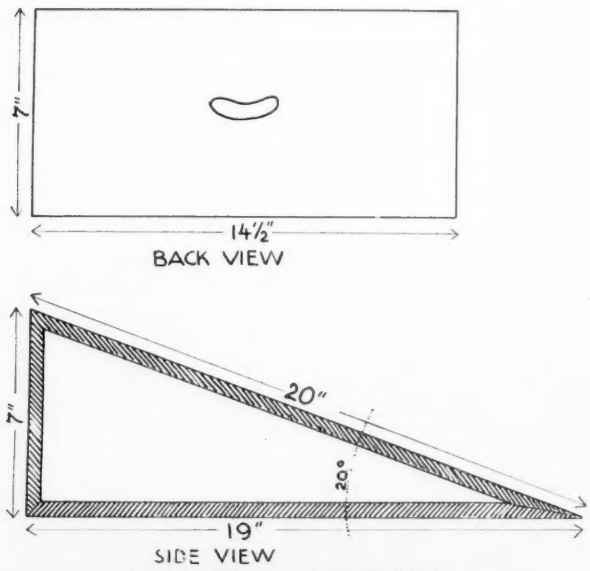

Fig. 4.—Diagram of angle block.

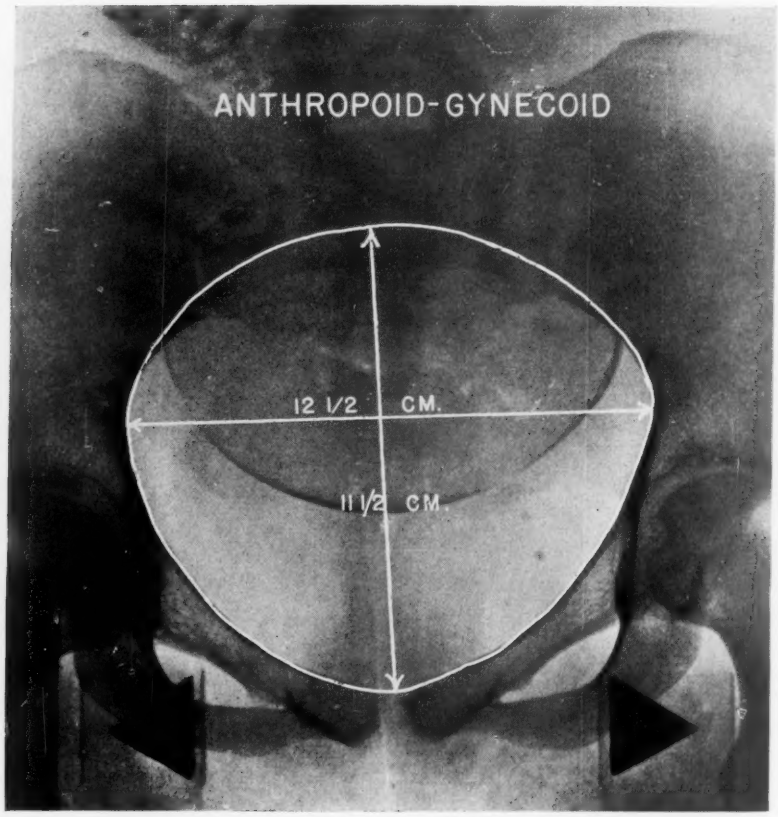

Fig. 5.—Radiograph taken with use of lumbosacral pad.

work is facilitated by the induced cooperation of the patient who is at ease in this posture. The plane of the inlet and film are unchanged.

The angle block is similar to the various angle blocks used for projections of the accessory sinuses or mastoids, being only a trifle larger. It may be used for such additional projections as gastrointestinal tract when unorthodox specified projections are requested or for projections of the thorax and might be considered useful in locating apical lesions with the patient recumbent.

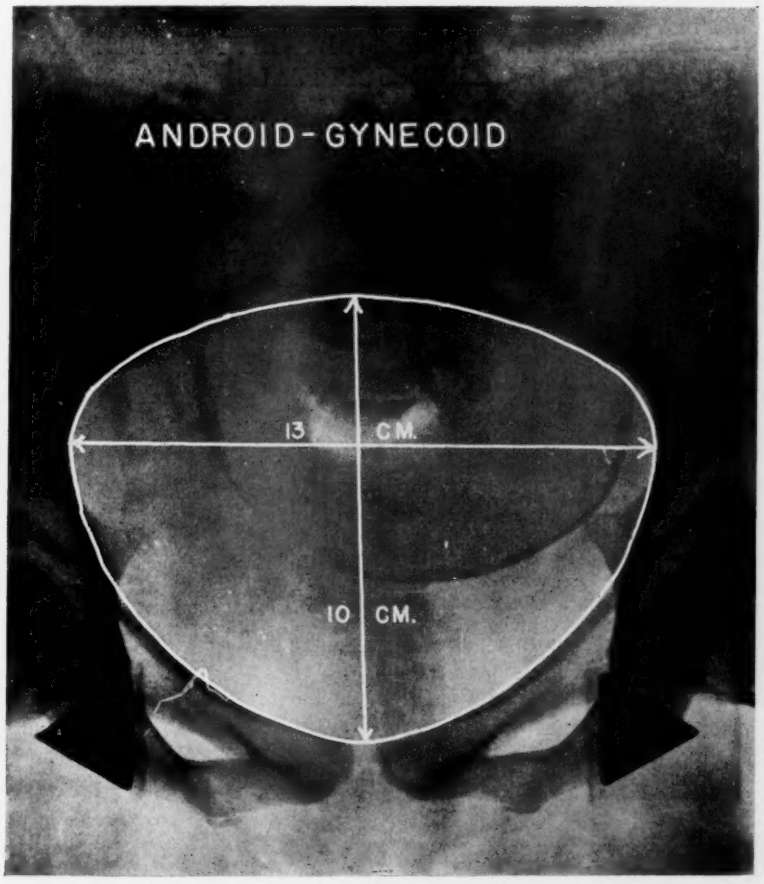

Fig. 6.—Radiograph taken with use of angle block.

As is the case in all angle blocks used for various projections, nails should be eliminated, strong but lightweight wood of good quality should be used. An opening of sufficient size to permit entrance of the hand is placed in the rear of the block to permit rapid and easy handling.

I wish to express my gratitude to Dr. S. A. Cosgrove, Medical Director and to Dr. H. J. Perlberg, director Department of Roentgenology for their review of this paper.

Department of Maternal Welfare

Conducted by Fred L. Adair, M.D., Chicago, Ill.

THE PROBLEM OF MATERNAL MORTALITY STUDIES IN THE SMALLER HOSPITALS

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DURING the past ten years the question of maternal mortality has been given widespread publicity and study. That this campaign, sponsored by lay groups and the profession, has done much to lower mortality rates is unquestioned. Statistics are being compiled by individuals and study groups which report marked reductions in certain causative factors of maternal mortality and point out other factors where further reductions can be expected.

The Pennsylvania State Maternal Mortality Committee, through its various committees, has done a monumental and worthwhile task in gathering together statewide statistics as to the cause of death in childbirth. Groups have been organized in the various larger cities to study maternal deaths and to determine the preventable factor in each case and assign the blame for the tragedy to whomever or whatever factor is responsible. If these study groups are worth while in Philadelphia, New York, and Chicago, why are they not just as worthwhile in smaller communities? The answer is they are, but that certain factors mitigate against their success in the small town.

In the first place, in small towns there are few and sometimes not any practitioners who are devoting all their time to obstetrics. It is too much to expect a busy practitioner, who is doing obstetrics along with a general practice, to be exercised over maternal mortality. He will read about it but promptly consign the article to the waste basket as a fad and continue to do things as he has done them for the past twenty years.

In the second place, in the average 200 bed hospital, the obstetric staff is composed of one full-time obstetrician, or none, with several busy practitioners who do general practice plus a large obstetric practice. Interest in a group discussion of fatalities in this hospital is difficult to arouse and difficult to maintain. The meetings are poorly attended and the physicians will not speak their minds because of the fear of arousing the ire of their fellow practitioners. In other words, the physicians in a small town know each other too well to give or take honest criticism.

In the third place, the average small hospital has a series of deliveries too small to embrace all the complications, and cases suitable for study occur too infrequently to maintain interest in a regular meeting. The study is sporadic and soon dies a natural death. Maternal mortality is a subject that must be kept continually before the profession if any good is to come of an organized study group.

What is the solution to the problem in our smaller communities? We think that we have solved these difficulties in part by our method of procedure. In this vicinity, we have four hospitals located in three cities all within an 18-mile radius. Hospital A has 800 deliveries a year; Hospital B has 750; Hospital C has 650; and Hospital D 700. This is a combined total of 2,900, which is a fair-sized number for statistical study and among which more complications and fatalities are bound to occur. Three years ago we organized the Lehigh Valley Obstetrical Society which was comprised of the Obstetrical Staffs of the four hospitals as charter members. The organization was very simple. We agreed to meet at the four hospitals in rotation every three months with the hospital staff at which the meeting was being held to be host to the gathering. It was agreed that each hospital staff would bring to the meeting the chart of each fatality that had occurred in that hospital since the last meeting. An effort was to be made to obtain data on deaths that occurred in the home from a puerperal cause, but these are surprisingly infrequent in that these patients are usually brought to the hospital when they become ill or the emergency becomes great enough. The attending physician is notified that his case is coming up for discussion and invited to attend the meeting. In most instances, he or she appears but is not named in the discussion so that very few of the group know whose case is being studied. The case is presented by a disinterested person and discussed from all angles to elicit a preventable factor and, if possible, to assign the responsibility for the fatality. The discussion is frank. If criticism of treatment or method of procedure is meted out in a particular case no one becomes angry because the audience is present to profit by its mistakes. We have had some very heated discussions, but I have yet to see a physician take offense at justified criticism. If the meeting is hampered by too few cases to discuss, the host then introduces a topic for discussion which has been agreed upon at the previous meeting. These topics are obstetric complications, such as disproportion, hemorrhage, etc., and charts are produced to illustrate treatment of these complications, diagnosis and treatment being stressed. Frequently a member of the group is permitted to display his hobby, and we have had some interesting obstetric photography, favorite techniques, etc.

The beginning was slow but the growth has been healthy. Our first meeting was attended by eight interested physicians. Since then our attendance has grown and now averages 40 to 50. Nursing groups now attend regularly, particularly nurses of the obstetric departments from the various hospitals in the group and the visiting nurses of the towns in which the hospitals are situated. That they are interested and benefit by the discussion is evidenced by the regularity and increasing number of the attendance.

We think that the program has made most of the members more careful in their work and judgment in complications. A number of the men have told me that when presented with a problem in diagnosis or a choice of procedure, they remember the discussion on similar cases and are doubly careful to prevent the particular case in which they are working from becoming the subject of discussion at the next meeting. Or if they are so unfortunate as to have to present their case, they will have done nothing or omitted no procedure for which they could be criticized. Thus a friendly rivalry has been growing between the staffs of the component hospitals to have the best record since the preceding

meeting. Surprisingly enough, the thought of presenting a fatality at one of our meetings is in the back of our conscience when we are treating complications or contemplating an operative procedure. This makes us "indication-conscious," if I may coin a phrase, and we are doubly careful to err on the side of caution and conservatism, all of which will benefit the patient and make for better obstetrics.

Another fact has emerged from our meetings. When we first discussed cases, we ended our discussion with the reading of the death certificate. It was evident that there were attempts by the profession to "cover up" a death; in other words, to so word the final diagnosis that it would look as if the patient had died from a complication which was unrelated to the puerperal state. Criticism of this fact has been so frank and open that it is very seldom we find the "cover up" attempted. Now we "call a spade a spade" and if a patient dies of sepsis or peritonitis we call it just that and resolve to be more careful in the future as to our techniques and indicated procedures.

We are attempting to standardize our charts and procedures in the four hospitals so that in the future we will have larger case series from which to obtain statistical data.

The whole setup has untold possibilities. We hope to work out interhospital consultation service so that one hospital may have the benefit of the wisdom and judgment of three other hospital staffs in problem cases. We have had interhospital inspection of the maternity departments in which the host staff proudly displayed new equipment and building additions. Criticisms have been invited and welcomed.

We have not as yet touched morbidity or fetal mortality in our discussions but plans are being formulated to take care of these phases of our work as soon as our charts are completely standardized.

We think that we have, in part, solved the problem of maternal mortality discussion in the smaller hospitals. The ever-widening scope of our meetings has created new, and renewed old, interest in a pertinent problem. The setup is applicable in most small towns where there are hospitals within comfortable driving distance of each other. The purpose of this paper is to bring our method of procedure to the attention of the profession with the hope that it will be tried in other small communities.

MATERNITY HOME CARE FOR UNMARRIED MOTHERS

A STUDY of the special institutions caring for unmarried mothers before and after the birth of their babies was included by the Children's Bureau as part of a social-statistics project during the years 1937 through 1940. Monthly reports were obtained from 84 institutions located in 37 urban areas; all maternity homes within each area were included. (*The Child,* Nos. 3 and 4, 1941.)

The number of institutions in these areas varied from one to five and the number of women under care in the total area maintained an average of approximately 2,000. During 1940 the total number of women cared for in these homes was 9,942, ranging from 62 in Akron to 981 in Chicago.

The number of women admitted to the homes per 100,000 population varied from 8 in Baltimore to 193 in Syracuse. In the middle half the rates were between 25 and 67. (The total birth rate for the country as a whole was 17.1 per 1,000 in 1937 with a reported illegitimate rate of

40.2 per 1,000 live births, making a total reported illegitimate rate of 68 per 100,000 total population.)

Those who were local residents of the reporting areas varied from 13 per cent in Sioux City to 90 per cent in Houston. The relatively low proportion of resident women cared for in some areas indicates that the service is available to a geographic area which is statewide and in some instances even wider.

The average length of stay of each individual was 94 days with a range of from 14 days in Syracuse to 174 days in Atlanta and Richmond.

Of the 84 maternity homes included in this series, 19 were under the auspices of Catholic agencies, 18 were affiliated with the National Florence Crittenton Mission, and 21 were under the auspices of other religious denominations, nonsectarian boards and a public agency. (It is significant that in only one instance was the institution tax supported.)

Attention should be drawn to the fact that maternity home care is only one part of the service provided for unmarried mothers in a well-organized plan for their needs and lacking in this study is information on case work services provided to unmarried mothers by family-welfare, child-caring and health agencies. Studies recently conducted in several areas have revealed serious gaps in the service available and have made it apparent that there is insufficient knowledge of the extent of the problem of unmarried parenthood in these areas.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

MENTAL DISORDERS ASSOCIATED WITH CHILDBEARING

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HISTORICAL

THE fact that mental disorder may complicate childbearing is an ancient observation. Hippocrates,[1] Celsus, Galen and Soramus[71,73] recorded instances of post-partum psychoses. Hippocrates believed that these were due either to suppressed lochial discharges, a diversion of milk from the breast to the brain, or to the influx of blood to the breasts and his theories of etiology persisted for centuries. Esquirol[2] believed that the mental disorder possibly could be due either to milk deposits in the brain or the sex of the child. In 1847, James Macdonald[4] reported a series of cases of "puerperal insanity" and maintained that a special form of insanity could be distinguished. He did not believe that suppression of milk had etiologic significance and pointed out that autopsies of such cases failed to reveal milk in the cranium or abdominal cavity. Marcé,[7] in 1858, was the first to challenge the traditional views and maintained that there was nothing specific about puerperal mental disorders and these did not differ from psychoses occurring in nonpuerperal women of the same age. Unfortunately, his contributions were disregarded for fifty years and physicians continued to believe that a specific type of "puerperal insanity" existed.

The literature[8-25] between 1860 and 1900 is filled with case reports of "puerperal insanity" which were further subdivided into "insanity of pregnancy," "puerperal insanity," and "insanity of lactation." This nomenclature was supposedly based on etiologic considerations. Thus, the psychoses of gestation were due to anemia, albuminuria, physical exhaustion, domestic unhappiness and fear of childbirth; those of puerperium due to pain, shock, infection, and hemorrhage and those of lactation due to exhaustion, anemia, and depletion by prolonged nursing. The predisposing cause for all types was primarily neuropathic heredity, but poor mental and moral training and illegitimate pregnancy were also considered significant. No attempt was made to classify the type of mental disorder except on the basis of the phase of childbearing in which it occurred. Since several types of mental disorder, each with its own prognosis, may occur in any phase of childbearing, it is obvious that their statistical tables were useless for prognosis. Inasmuch as no such nosologic entity as "puerperal insanity" exists, there appears to be even less reason for such terms as "gestational," "puerperal," and "lactational" insanity.

From 1900 to 1915, various authors[26-44] demonstrated that no specific mental disorder occurred in relation to childbearing. The literature of this period is largely concerned with the re-classification of these puerperal mental complications into the regular scheme of psychiatric diagnosis.

INCIDENCE

The exact incidence of mental disorders associated with childbearing is unknown. Numerous attempts have been made[10, 21, 26, 28, 43, 44] to ascertain their rate of occurrence but reports differ greatly. Estimations of the number of women admitted to mental hospitals because of puerperal mental disorder have varied from 3.1 per cent to 21.6 per cent. The majority of statistics indicates that about 8 per cent of female admissions to mental hospitals are because of mental illness associated with childbearing. This figure does not give the real incidence since many women have a mild, transitory psychosis or toxic delirium from which they recover at home or in a general hospital and are therefore not included in the mental hospital statistics.

Attempts have been made to approach this problem of incidence from another standpoint, namely, the frequency of puerperal mental disease in relation to the total number of deliveries. The findings of different observers have been in total disagreement and have varied from 1 psychosis in 80 deliveries[10] to 1 in 2,000.[34] This wide discrepancy has never been satisfactorily explained although various authors have believed that the illegitimacy rate of the community, the economic level of the patients, social unrest and war, the physical health standards of the group and many other factors might explain the wide variation. In short, the relative frequency of mental disorders and the number of deliveries is unknown and all existing figures have failed to include those cases developing insidiously after convalescence from delivery. The accepted rate is 1 complicating mental disorder in 400 deliveries, but this figure has little except tradition to support it.

THE NATURE AND CAUSES OF PUERPERAL MENTAL DISORDERS

Mental disorders, rather than constituting disease entities, are better understood as inferior and maladapted patterns of reaction designed to meet biologic, social, and personal problems confronting the individual. Different individuals possess variable quantities of psychic reserves with which to meet various social, physical, and psychologic stresses. If these threats to mental integrity are minimal or the psychic resistance and reserves are optimal, the individual remains "normal." However, some individuals have a paucity of psychic assets or are subjected to an overwhelming load and are unable to cope with the situation in the usual and expected manner. They respond to stress with behavior patterns that are poorly adapted for efficient social adjustment and are therefore termed "abnormal." The exact type of abnormal pattern of reaction will depend on many factors, some constitutional in nature and others which are determined by the individual's training, experience, habitual modes of thinking, and emotional problems and conflicts.

From a psychiatric viewpoint, childbearing constitutes a difficult life situation which imposes physical, physiologic, psychologic, and social stresses upon the pregnant woman. To remain "normal" she must react to these in the usual and accepted manner and not allow underlying

emotional problems and conflicts to appear in symbolic forms and abnormal behavior which are unrestrained by the demands of reality. Pregnancy is often a test of the stability of the personality and even an uneventful gestation imposes heavy burdens on the patient's psychic organization. Any disturbing factor, whether a mental conflict, toxemia or social unrest, will lessen the patient's capacity to control her emotional difficulties and constitutional tendencies to some form of mental disorder.

The physical and physiologic disturbances of the average gestation are myriad in number, every part of the maternal organism reacting in the complete metabolic reorganization of pregnancy. While in the midst of this physiologic reorganization, the pregnant woman is subjected to other disturbances which further exhaust her psychic and physical reserves. During the late months of gestation, she has difficulty in securing sufficient rest. Usually she has backache and nagging pains which are irritating and exhausting. Mild toxic states occur which disturb the patient's equilibrium without producing obvious clinical manifestations. At the time of delivery, tremendous demands are made on the patient's capacity for physical readjustment to meet the shock and exhaustion of labor, hemorrhage and multiple thromboses, laceration and infection, and toxicity from hypnotics and anesthetics. Following delivery, another major metabolic readjustment must be made including involution of the reproductive organs and initiation of lactation. Further physical depletion occurs when the mother assumes the care of the child and resumes her household duties. However, none of these factors acts as a specific cause of mental disorder. These are the predisposing causes which operate by so reducing the clarity of consciousness and the powers of repression and self-control that underlying conflicts, problems, and constitutional tendencies are expressed in pathologic behavior and thought. In view of these facts, it is interesting to note that nearly all observers have reported that only a small proportion of their patients have had a history or evidence of unusual physical depletion. It would appear that physical causes are not of major significance except in cases of toxic delirium.

The possibility that endocrine changes of pregnancy might play an important etiologic role has received serious consideration.[81, 90, 95, 98] At the present time, there is little definite data regarding the relationship between the hormonal tides and psychologic reactions and objective studies[106] have only recently been undertaken. In addition, Karnosh and Hope[98] made prolan estimations and quantitative estrin studies in ten cases of post-partum psychoses and found low normal values which did not differ appreciably from those of nonpsychotic puerperal women. The widespread therapeutic use of hormone preparations in mental disorders has only added confusion to the problem of the role of the endocrine glands in the production of psychiatric disorders. Unfortunately, a few publications have appeared which credited one or another hormone preparation with miraculous specific therapeutic action in "puerperal insanity," but evidence was not presented to show that these results were not due to suggestion or to the coincidental remission of a self-limited psychosis. For the present, it may be admitted that marked changes occur in the endocrine functions during pregnancy, but there is no conclusive evidence to show that this is of specific significance in the production of puerperal mental disorders.

Nearly all writers have agreed that psychologic factors are the most important in the etiology of puerperal mental disorders. Childbearing has a psychic significance[66, 78, 83, 100] as well as physiologic aspects. This important epoch calls forth many emotional attitudes, the nature of which will depend upon the patient's personality and patterns of thought and feeling. Every woman must undergo a mental reorganization in her pregnancy in reaction to this new life situation. The period of gestation has been known traditionally as a time of feminine irritability, emotional instability, and unpredictability. Some of this may be in reaction to underlying emotional problems but physical discomfort, nagging aches and inconveniences will also contribute. Individuals differ in their ability to tolerate discomfort and the less stable react with exaggerated emotional responses. Of greater importance, however, is the patient's reaction to childbearing as a significant milestone in her life. It will mean that her period of carefree youth is ended and adult responsibilities must now be assumed. For some women the pregnancy may represent the cementing of an unsatisfactory marriage and will mean that she is now morally and economically bound to a shiftless, unstable husband. Selfish women resent the fact that they will no longer be pampered but now must share the husband's love and attention with a newborn rival. Vain and self-centered patients who are in need of constant adulation often become emotionally disturbed by the fear that pregnancy may cost them their beauty. Physiologic capacity for pregnancy is not always accompanied by a corresponding psychologic maturity necessary to meet the emotional problems incurred by childbearing.

In some patients it is not unusual to find mental conflict over moral issues concerning pregnancy because it represents the culmination of their sexual life. Many women of strict background and training have been taught that the sexual aspects of life are disgusting and degrading even in marriage. One who has been taught that pregnancy is the supreme punishment for sin and sexual misbehavior will have difficulty in accepting gestation without deep feelings of guilt. Thus, some women have uncontrollable emotions of shame and embarrassment during pregnancy because of the feeling that others regard them as guilty of wrongdoing. In some, powerful conscious and unconscious sexual conflicts are revived and cause severe emotional unrest. These considerations suggest that patients impregnated extramaritally would be especially prone to emotional conflicts over sin but, paradoxically, most writers report that such moral issues are more common in married women. The sexual life of patients with puerperal mental disorders has been studied,[71, 72, 85, 107] and it has been found that 60 per cent of puerperal manic-depressive and schizophrenic women were frigid in marriage, but the same proportion is reported[85, 107] in nonpuerperal psychotic women. It appears that a large percentage of these women have been unable to reach an adult, mature sexual level. However, instead of this operating as a specific etiologic factor, it is more probable that this only represents an index of their emotional immaturity and incomplete personality development which renders them more liable to mental disturbances.

Another psychologic factor of importance is the attitude of anxiety and fear of some patients approaching delivery. Some women have a personality which is poorly organized to tolerate pain and adversity. Many have been sheltered from the realities of life and in pregnancy

find themselves confronted with the first problem that their parents cannot solve for them. Frightened by old wives' tales and having no experience in fortitude, they approach term with terror and despair and only a minor event is necessary to precipitate a major mental crisis.

Economic and social factors also play an important part in shaping the attitude of a pregnant woman. She is in a particularly helpless condition and not able to meet sudden social and economic dislocations. During the Napoleonic wars, the occurrence rate of puerperal psychoses increased rapidly,[2, 3] and this rise was out of proportion to the general trend of female admissions. More recently, Karnosh and Hope[98] have demonstrated the same disproportionate increase during the depression. Economic insecurity and social unrest add to the difficulties of a pregnant woman, and she must face the fact that her gestation will end with a new problem of caring for another child.

In the majority of cases it is impossible to demonstrate a major, dramatic psychologic trauma which has served as the exciting cause of a puerperal mental disorder. Rather, the minor nagging worries and difficulties seem to have a cumulative effect, especially in multiparas. Some women find their life monotonous, meaningless, and punctuated only by frequent episodes of childbearing. For them, another pregnancy may represent an intolerable life situation in spite of previous easy and uncomplicated deliveries.

In short, puerperal mental disorders are due primarily to psychologic causes but social, physical, and toxic factors play a part in the release of underlying reaction patterns. Whether or not a mental disorder will appear in association with childbearing will depend upon a personal equation which is different for each patient. It might be formulated: Is the patient's psychic reserve (hereditary constitution, training, personal psychologic organization) sufficient to resist the factors producing mental disorder (toxicity, endocrine imbalance, psychologic conflicts engendered by pregnancy)? Thus, a patient of poor personality organization may become mentally ill in spite of excellent physical health and few apparent socioeconomic-psychic problems, while another individual of more sthenic personality structure passes mentally unscathed through the most adverse and complicated circumstances of childbearing.

Finally, it is necessary to differentiate between mental disorders complicating childbearing and pregnancy complicating a psychotic episode. Certain patients have recurrent episodes of mental illness during which pregnancy occurs in a coincidental relationship. Others conceive as a result of indiscretions or heightened eroticism due to mental disorder. For example, an unmarried woman was diagnosed as having a puerperal mental disorder but investigation proved that the sexual relationship and conception occurred as a result of mental confusion associated with an advanced schizophrenic psychosis. The coincidental occurrence of pregnancy and mental illness does not establish childbearing as the prime etiologic factor.

TIME OF ONSET

Although no diagnostic or prognostic conclusions can be reached by ascertaining whether the complicating mental disorder began during pregnancy or during early or late puerperium, it is still of value for the obstetrician to know which periods are the most dangerous from the psychiatric standpoint. The literature (Table I) reveals consider-

TABLE I. TIME OF ONSET OF THE MENTAL DISORDER

AUTHOR	PREGNANCY PER CENT	PUERPERIUM PER CENT	POST-PUERPERAL PER CENT
Macdonald,[4] 1847	6.0	66.0	27.0
Hengst,[9] 1878	18.0	47.0	35.0
Ballintine,[38] 1909	12.0	74.0	14.0
Sandy,[40] 1913	15.0	28.0	57.0
Bear,[55] 1921	20.0	63.0	17.0
Riggs,[56] 1922	11.3	46.4	42.1
Armstrong-Jones,[59] 1923	22.0	44.0	33.0
Bourne,[62] 1924	6.0	60.5	33.5
Cruickshank,[109] 1940	16.0	84.0	
Median and average estimates	14.0	54.0	32.0

able disagreement concerning this point and this may be due to the different limits assigned to the puerperal period by various authors. One writer classifies all psychoses occurring within two or three months as "puerperal" while others designate any disorder after the lying-in period as "lactational." For this reason, the statistics supply only an estimate of the frequency of mental disorders in these various periods. An average of sample statistics throughout the years suggests the following frequency distribution: Pregnancy 14 per cent, early puerperal (the first 14 days post partum) 54 per cent, late puerperal 32 per cent. These figures have little claim to mathematical exactitude and have value only as indicators of the most vulnerable periods for the onset of mental disorders.

RELATIONSHIP BETWEEN MENTAL ILLNESS AND PARITY

There has been considerable disagreement whether mental illness is more prevalent in primiparas or multiparas, and many conflicting reports could be cited. This disparity is due to the practice of comparing the frequency of psychoses in the two groups without reference to the disproportion in the number of primiparous and multiparous pregnancies. Mental disorders of all types are probably slightly more frequent in multiparas, but the difference in the proportionate rate of occurrence in the two groups is not great.

DIAGNOSTIC CLASSIFICATION

The mental disorders associated with childbearing can be classified readily in the ordinary scheme of psychiatric diagnosis, inasmuch as they do not differ in symptomatology or prognosis. Table II records the frequency distribution of the various psychoses in series of cases reported by different authors. There is some variation in the percentages of each disorder but the figures are in general agreement. A median and average estimate suggests the following gross distribution of diagnoses: Manic-depressive psychosis 40 per cent; schizophrenia 20 per cent; delirium 28.5 per cent; psychoneurosis 6 per cent, psychosis with psychopathic personality 5 per cent. Other types of mental illness, such as general paresis and alcoholic psychoses, may occur but they are infrequent and only coincidental.

MANIC-DEPRESSIVE PSYCHOSES

Manic-depressive psychoses, especially those in the depressive phase, are the most common of the puerperal mental disorders. The ultimate

TABLE II. DISTRIBUTION OF TYPES OF MENTAL DISORDER

AUTHOR	MANIC-DEPRESSIVE PER CENT	SCHIZOPHRENIA PER CENT	DELIRIUM PER CENT	PARANOID CONDITION PER CENT	EPILEPTIC PSYCHOSIS PER CENT	ALCOHOLIC PSYCHOSIS PER CENT	GENERAL PARESIS PER CENT	PSYCHOSIS WITH MENTAL DEFICIENCY PER CENT	PSYCHOSIS WITH PSYCHOPATHIC PERSONALITY PER CENT	ACUTE TRANSITORY EXCITEMENT PER CENT	PSYCHONEUROSIS PER CENT
Ballintine,[38] 1909	24.5	35.0	26.6		2.1	1.4	2.8				5.6
Sandy,[40] 1913	53.0	17.0	26.0	3.0 (1 case)							
Gregory,[60] 1924	45.0	16.0	28.0		3.0	1.0 (1 case)		1 (1 case)		5	
Strecker,[66] 1926	36.0	26.0	34.0				2.0				2.0
Kilpatrick and Tiebout,[110] 1926	49.0	13.0	34.0								4.0
Smalldon,[107] 1940	48.1	28.8	3.6	0.45 (1 case)					5.4		12.6
Cruickshank,[109] 1940	33.0	26.0	38.0					1			1.0
This series (150 cases)	31.2	17.6	28.8		1.6		1.6		4.8		14.4
Median and average estimates	40.0	20.0	28.5	1.0					5.0		6.0

cause of this disorder is unknown but various psychologic, biochemical, and endocrinologic causes have been suggested. Although final etiologic conclusions cannot be reached, it is agreed that this psychosis is most likely to occur in people of a certain personality pattern termed the "syntonic temperament." Individuals of this type direct their energies and interests into the outside world rather than inwardly into their own mental life. Usually they are warm, tender, and sympathetic, responding emotionally in harmony with others and their environment. These individuals are often lively, energetic and socially active although some, because of shyness and lack of aggressiveness, give the impression of timidity and withdrawal. The whole group oscillate between the poles of warm, infectious gayety and unobtrusive, taciturn somberness. Under the stress and pressure of psychologic conflicts or physiologic changes, it is possible that the underlying cyclic emotional swing may be so widened in amplitude that it constitutes obvious mental disorder. In the cases under consideration, pregnancy with its associated problems supplies the extra strain. Whether the patient's reaction will be manic or depressive in nature depends on unknown factors, but it has been suggested that unconscious personal problems, situational setting, and habitual modes of response decide this issue.

Once the manic-depressive reaction pattern is established it tends to recur when the patient is again under psychologic or physiologic stress. Thus, the initial attack may occur in association with childbearing, and repeated psychotic episodes appear in subsequent gestations. Cases have been reported in which twelve manic-depressive reactions ensued in as many pregnancies, the patient remaining mentally well in the interpuerperal intervals. On the other hand, although the syndrome may first appear in association with pregnancy, it may assume an independent existence and further attacks occur without reference to childbearing. Finally, the patient who already has an established, recurrent manic-depressive cycle is likely to have an attack during the puerperium, the pregnancy acting as a nonspecific stressful situation. In some cases, the gestation may appear to be an important etiologic factor; in others, it seems to be merely a coincidence.

MANIC REACTIONS

Manic reactions are infrequent during gestation. During this period an occasional hypomanic episode may be observed but a full-blown manic reaction rarely occurs unless the predisposition is marked or the patient has had previous attacks.

The most usual time of onset is seven to fourteen days post partum. During pregnancy there are frequently premonitory signs such as unusual nervousness and tension, flightiness or apprehension. The onset is usually abrupt after one or two days of prodromal excitement, garrulity and restlessness, although a short period of depression may precede the manic outburst. The clinical picture is characterized by extreme excitement, rapid flow of thought, grandiose ideas, and motor overactivity. Often there is considerable confusion and unclearness suggesting a toxic factor, but this usually disappears after a few days, leaving a relatively pure manic reaction. Actual states of toxicity may be engendered by the overactivity and diminished fluid and food intake, thus superimposing delirious reactions upon the underlying mania.

CASE 1.—A married woman, aged 33 years, para iii, gravida iv, was admitted to the hospital because of uncontrolled restlessness, talkativeness, and bizarre

behavior. She was in the seventh month of gestation, her mental symptoms beginning during the fifth month. At this time she became highly elated, talked constantly in a flighty manner and expressed grandiose ideas concerning her ability, beauty, and desirability. She gave away her children's clothing, made many foolish, expensive purchases, and ran away from home on several occasions. Before admission she suspected her husband of infidelity and thought that he was not interested in the home. There was no basis for these suspicions, and they appeared to be projections of her own attitudes.

Physical examination revealed a well-developed, well-nourished woman without evidence of organic disease. All laboratory studies were consistently negative. Obstetric examination revealed a normal pregnancy. She delivered a normal child at term without complications.

During her hospital residence the patient was elated, overactive, and talked constantly with a flight of ideas, usually expressing dissatisfaction with her marital situation. Often she sarcastically referred to her husband, ridiculing his intelligence, appearance, cultural standards, and earning ability. She projected her own conflicts upon him, stating that he did not care for her, he wanted to be with other people, and, "He dislikes me because I get pregnant so often and he made insulting references about the source of my pregnancy." At all times she was correctly oriented and clear in comprehension. A diagnosis was made of: Manic-depressive psychosis, manic phase, third attack.

The family history was negative for mental abnormality. The patient's history revealed no serious illnesses. She had completed a common school education and was an intelligent woman who felt confined by the limitations of a small town. Her personality pattern was described as sociable, aggressive, and ambitious. At the age of 24 years she married a plodding, mediocre individual and delivered her first child within one year. Ten days after this delivery, she became restless and talkative, referred to her husband as an enemy and expressed grandiose delusions concerning herself and her future prospects. At times she tore off her clothing, destroyed household furnishings, screamed and laughed loudly, and was disheveled in appearance. This behavior continued for five weeks and eventuated in recovery. No unusual mental manifestations were apparent during the second or third pregnancies. Two years before the present admission she had measles and influenza, and a second manic attack, four weeks in duration, complicated this illness.

The present episode subsided after delivery but reappeared as soon as she returned home. She became noisy and overactive and refused to live with her husband, at times threatening to kill him. This attack lasted one year and was so severe that state hospital care was necessary. After apparent recovery, she was informed of her impending discharge from the hospital in the care of her husband and another short manic episode occurred immediately. Following parole from the hospital, she separated from her husband and children and established a home in a large city. She apparently remained healthy and happy for twelve years until another manic attack necessitated return to a mental hospital.

It is usually difficult to manage these patients, and they create a problem on the obstetric ward because of their noisiness, intractability, and inability to cooperate in the nursing regime. Often they become exhausted, malnourished and dehydrated, and incur dangerous infections. It is imperative to maintain a high caloric intake and adequate fluid balance by mechanical feeding or intravenous infusions if necessary and to secure sufficient rest by means of sedatives. As soon as the obstetric condition permits, the patient should be transferred to a psychiatric hospital for continued care.

DEPRESSIVE REACTIONS

Although depressive reactions do not present such startling and dramatic symptoms as the manic phase, they constitute an equal or greater hazard to the life of both the mother and child. Often the

family and physician overlook or minimize post-partum depressive states, especially when there has been an obvious precipitating sad event, and regard the patient's behavior as "natural grief" and are surprised to find that this reaction has quietly progressed to a deep depression.

The time of onset is from a few days to a few weeks after delivery; only a small minority of cases occur ante partum. Occasionally, the depressive reaction begins rather abruptly with initial symptoms of confusion, perplexity, and apprehension and then shifts to an obvious mental depression. In other cases the onset is insidious, progressing almost imperceptibly from a mild discouragement to a deep depressive state. Coincidental or precipitating toxic reactions may be noted in the early phases, but these soon disappear as the physical condition improves, disclosing the major underlying depressive trend.

The clinical picture is characterized by physical and mental lethargy, retardation of thought and action, sadness and self-accusations of unworthiness and wrongdoing. The outstanding feature is the emotional depression and the sense of futility. This leads to a loss of appetite or unwillingness to take nourishment and fluids, and secondary malnutrition, dehydration, and toxicity often occur. The clinical course of such a patient is shown in the following case:

CASE 2.—A married woman, aged 22 years, para ii, was admitted to the hospital three months after her last delivery because of mental depression, ideas of great unworthiness and physical failure. Her obstetrician stated that her health had been excellent throughout gestation. Delivery was spontaneous following five hours' labor and no complications occurred. She was delighted with the child and was in excellent spirits until the sixth day when she suddenly began to cry, fearing that she was to die. Her physical health continued to be excellent, and she was discharged from the obstetric ward on the eleventh day. The mental depression deepened and was accompanied by a slow physical failure due to refusal to eat or otherwise attend to her bodily needs. She lost 20 pounds in weight.

Physical examination revealed a poorly nourished woman who appeared to be acutely ill. The skin was flushed and greasy and an acneform eruption covered the face. The eyelids and lips were swollen. No definite physical disorder could be detected. Laboratory studies were negative.

The patient's facial expression was one of complete dejection and hopelessness. She talked slowly in a subdued, monotonous voice, expressing ideas of great unworthiness and sin. Usually she maintained that she was "no good," that the pregnancy had been a mistake, that the baby "wasn't all right," and that she had sinned by bringing him into the world. She wanted to die, yet was afraid that she would. Her sin had made the whole world suffer, especially her husband and children. The patient stated that her mind was flooded with such feelings of sadness and despair that it was impossible to think of anything except the enormity of her sins. Occasionally, voices taunted or questioned her about wrongdoing.

The patient's physical condition improved slowly. Soon she was able to be placed in a chair where she sat motionless, her head bowed, completely disinterested in everything except her own sad thoughts. Improvement in the mental condition occurred slowly during the next two months; the ideas of unworthiness gradually disappeared, and she again became interested in return to her husband and children. The total duration of her mental illness was six months and she was eventually discharged as recovered. The diagnosis was: Manic-depressive psychosis, depressed phase, first attack.

The family history was negative for mental abnormality except that her father was heavily alcoholic and irresponsible. The patient's history revealed no serious illnesses or accidents. In personality she was considered to be shy, sociable, fun-loving, and occasionally high tempered. At the age of 15 years she left home to work in a large city, and while there had been intimate with at least three men and had contracted syphilis. She returned home and married without mentioning her

previous experiences. The marital adjustment was fairly good but the economic adjustment was always precarious, the family receiving Welfare aid for the past two years. During the last pregnancy, the patient had quarreled with the husband because of his absences from home and his inability to support her.

After recovery the patient stated that on the sixth day post partum, she had experienced an intense anxiety and fear that she would die. She believed that this idea had been suggested by hearing the howling of a dog. Immediately afterward she heard voices discussing her premarital sexual promiscuity and syphilitic infection, and once she thought she saw the devil pass by her door. Later she imagined hearing her husband's voice asking about her misconduct, and she actually confessed to him, hoping to relieve herself of the awful feelings of guilt. This brought no relief and she continued to ruminate constantly about her sins and the possible syphilitic infection of her children. These guilt feelings became more severe when she recalled that she had allowed pregnancy to occur in order to force her husband to stay home nights with her. She stated that during the early months of her mental illness she often thought of destroying herself and the children to avoid the horrible fate that awaited all of them.

It is of paramount importance that the depressive state be recognized early so that suitable treatment and precautions may be instituted. The physical health of these patients declines rapidly and mechanical feeding or intravenous infusions should be used if the patient is unable or unwilling to take sufficient nourishment and fluids. Often these patients are unable to sleep at night and occupy themselves with horrible thoughts; in these cases sedation should be employed to supply necessary rest and prevent exhaustion. Elimination by bowel is usually impaired and cleansing enemas should be administered regularly. Inasmuch as she will be unable to nurse the child, necessary attention should be given to the breasts. As soon as the obstetric condition permits, the patient should be transferred to a suitable psychiatric hospital.

The greatest hazard is the constant danger of suicide and/or infanticide. These patients often believe that their condition is hopeless, that they and the children are doomed to everlasting suffering and that death is preferable to their mutual prospect. Suicide may be accomplished with the most meager apparatus and, therefore, everything of lethal potentiality must be removed from the room, the windows strongly screened and constant nursing supervision maintained. The child should not be allowed in the room and under no circumstances should the mother be alone with the baby. The possibility of suicide and infanticide in depressed patients cannot be overemphasized, since it is in this group of cases that self-destruction and child murder are most likely to occur.[20, 69, 88, 89]

The prognosis of puerperal manic-depressive psychoses is usually quite good. If this is the first attack the patient almost invariably recovers after a few months. Only a few develop permanent persecutory syndromes. If there have been previous attacks, the present disorder will probably be longer and more severe than the preceding episodes. Further pregnancies may or may not be complicated by repeated attacks, depending upon associated factors.

SCHIZOPHRENIA

Schizophrenia or dementia praecox comprises about 20 per cent of psychoses associated with childbearing. This pathologic reaction pattern appears most frequently in individuals of a certain psychologic constitution designated as the schizoid personality. A schizoid person is characteristically cold and reserved, living within himself and avoid-

ing close contact with his fellows. Often shy and timid, he finds solace in daydreams and attempts to shield himself from emotional situations. These individuals are sensitive and easily hurt but hide their feelings beneath a reserved, unemotional exterior. They often have deep attachments binding them to their parents and experience considerable difficulty in transferring their affection to others and attaining an adult, mature, emotional relationship. The schizoid person is a perfectly normal type but schizophrenia may develop in individuals of this personality pattern who are not able to meet the demands of reality. The exact etiology of this disorder is unknown but apparently it represents a withdrawal from reality into a childlike world of fantasy, symbolism, and disconnected, fragmented thought. The withdrawal may be so slow and imperceptible that it is difficult to determine when it began, but usually the final break is ushered in by an acute excited episode. In this phase the patient entertains bizarre delusions, hears imaginary voices, and his mental processes are confused and disorganized. This acute episode occasionally terminates in complete or partial recovery but more usually progresses to advanced mental deterioration. Most psychiatrists believe that this pathologic reaction pattern occurs because of the individual's inability to meet the exigent demands of reality which, in the present cases, are represented by the problems and vicissitudes of childbearing.

The majority of puerperal schizophrenics have a typical history of aloofness and introversion. They have preferred to remain emotionally bound to their parents and have had few, if any, love affairs of any consequence. Often they married their first and only suitor after a long, lukewarm courtship and many were so reluctant to marry that familial pressure was necessary. Their reaction to marriage was unenthusiastic and the majority were sexually unresponsive, finding marital intimacies aesthetically distasteful. While the general marital adjustment may be fairly satisfactory, it is apparent that the wife has not attained a psychologic sexual maturity and a full emotional relationship with her husband.

During gestation these patients are often morose, irritable, and flighty, and these symptoms may progress to a schizophrenic episode before term. Usually these manifestations are disregarded by the physician and family and ascribed to the "nervousness of the pregnant woman." After delivery it is noted that at times the patient appears odd, preoccupied, and uncertain in her behavior and makes occasional illogical and meaningless remarks. Her attitude toward the husband and child is frequently that of disinterest or open antagonism. Often these peculiarities are not outstanding and the acute psychotic episode, which may appear a few days after delivery or be postponed for several weeks, is completely unexpected. The mental manifestations correspond to those usually seen in schizophrenia. In addition, frequently the patient openly expresses her dissatisfaction with her husband and symbolically reveals her attitude toward the child by fearing or dreaming that he has been lost, kidnapped, or killed, or by denying her marriage and pregnancy. The excitement and associated refusal of food and fluids may cause a febrile and toxic reaction which sometimes leads the physician into making an erroneous diagnosis of a primary toxic state with secondary delirium. The following case is fairly typical.

CASE 3.—A married woman, aged 21 years, para i, was admitted to the hospital because of violent, disturbed behavior. The mental symptoms began four days after delivery. Her health was excellent during gestation and the delivery was easy and

uncomplicated. On the fourth post-partum day she had an unexplained fever of 102° F. for three hours. She became irrational, saw snakes and rabbits in the room, and believed that poison had been placed in the food. The mental disorder continued without abatement until her admission three weeks after delivery. No further physical complications had occurred.

Physical examination revealed a well-developed, well-nourished woman who did not appear to be acutely ill. Physical, gynecologic, and laboratory examinations were negative for organic disorder.

The patient's facial expression was that of passivity and disinterest. There was no clouding of consciousness or memory disturbances. At times she appeared perplexed but more usually she was indifferent and apathetic. Her answers to questions were vague and inadequate, and she frequently stared blankly into space. Blocking and disorganization of ideas were apparent in her stream of thought. The most outstanding characteristic was the dulling of emotions, and she was quite indifferent to her surroundings and the possibility of returning home. She never asked about the baby except to say, "I wouldn't cry much if something happened to my husband or the baby." On another occasion she stated that if her husband were to die she would marry a much nicer man, although this statement was quite irrelevant to the topic under discussion. Occasionally she muttered vaguely to herself about losing her beautiful figure. Auditory hallucinations occurred constantly, and she was frequently found sitting quietly, vaguely fumbling with her hair and staring vacantly into space while listening to her schoolgirl friends whispering to her.

This apathetic state alternated with periods of disturbance. During these episodes she was quite unpredictable, often suddenly assaulting those about her without provocation. She suddenly struck a nurse saying, "Don't say that, I'm no Christ." Often she tore off her clothing, shouting that her body was cowlike or that a married man was trying to seduce her and her sister. On occasions she was found in sexual postures as if carrying out imaginary relations. During the most excited period she decorated her hair with bloody rags.

The family history of this patient was completely negative. In personality, she had been a quiet, solitary, shut-in type of individual who had few friends. She was self-willed and irritable and had moody episodes when faced with any difficulty. She married the first and only man with whom she had dates. Conception occurred within the first three months, much against the patient's wishes.

The patient's further course was that of rapid physical and mental decline. She lost 15 pounds in weight in two months in spite of tube feeding. She became untidy in appearance, silly and deteriorated in her behavior, and spent her time laughing and shouting in response to imaginary voices. This reaction pattern continued after transfer to a state hospital where she died eight years later of pulmonary tuberculosis. The diagnosis in both hospitals was: schizophrenia, hebephrenic type.

In the present series of cases a few of the patients had psychotic symptoms early in pregnancy; some became suspicious and perplexed just before term but the majority had an acute onset within ten days post partum. These schizophrenic patients were divisible into two main types. In the first group were those individuals whose first psychotic break was severe and permanent, necessitating state hospital care. The second included patients who had had a previous mild or severe schizophrenic episode from which they had made an incomplete recovery. They had been able to live in the community but were queer, eccentric, emotionally cold individuals who evinced little interest in their homes, husbands, or children. Each succeeding pregnancy caused a severe exacerbation of their chronic psychosis and added an increment to their mental disorder until finally state hospital care became necessary. These latter cases clearly demonstrated the danger of allowing further pregnancies to occur in a woman who has had a puerperal schizophrenic psychosis.

The diagnosis of schizophrenia implies a very serious prognosis and the majority of these patients progress to a severe mental deterioration. The chances of recovery are about 1 in 4 or 5 and even if apparent recovery occurs there will usually be some residuals (emotional blunting, eccentric behavior, marital maladjustment). However, when schizophrenia occurs in relation to childbirth, it appears to have a slightly better outlook than in ordinary cases. This may be due[107] to the fact that the majority of cases are of the catatonic type, which regularly has a better prognosis, or because the disorder is precipitated by a specific difficult life situation. It is not unusual to see a surprising improvement in severe cases of puerperal schizophrenia and a poor prognosis should be withheld until the patient is well-advanced in the chronic phase.

DELIRIOUS REACTIONS

The toxic-exhaustive delirious states constitute about 28.5 per cent of the puerperal psychoses. These cases were quite frequent before the present era of aseptic obstetrics and the older physicians, noting improvement in the psychosis some time after an abscess was evacuated or some other toxic or exhausted state had disappeared, concluded that all puerperal mental disorders had a similar toxic-exhaustive origin. Some few still hold to this concept and fail to recognize the human personality factor in the production of a mental illness. The fact that some individuals pass through the most severe types of intoxicating processes without the appearance of a psychosis suggests that a personal psychologic predisposition plays an important role. Actual investigation reveals that many of these delirious reactions occur in patients who are laboring under such severe psychologic stresses and conflicts or who have such unstable personality organization that any physiologic or emotional crisis precipitated a delirium. Many of the delirious patients in this series were recognized as unstable, maladjusted persons long before their pregnancy. The psychologic resistance to delirium is no less real than the physical immunity to infection.

The delirious reactions are usually precipitated by infections, toxemias, excessive hemorrhage, severe exhaustion, and metabolic intoxications which cause a clouding of consciousness, hallucinatory states, and the release of underlying conflicts in a symbolic form. The amount of toxicity and exhaustion necessary to produce a delirium will depend upon the personality organization and life situation of the individual patient. What may be a negligible toxicity in a happy, stable woman will be overwhelming to a patient whose ordinary life burden taxes her to the limit. In short, the mere presence of toxicity or exhaustion will not invariably cause a delirium but, instead, the toxic-exhaustive factors and the personality problems confronting the patient must be weighed against the individual's psychic resistance. Viewed in this light, the delirious patients in the present series could be divided into two groups:

1. *The Toxic Deliria.*—This reaction occurred most frequently in women of considerable stability who had shown an average ability to manage the problems of their lives. Many had had previous uncomplicated pregnancies. However, in the present pregnancy some severe toxic state had occurred with the subsequent appearance of delirium. Such an intoxication may occur at any time during gestation or the puerperium, but it is most commonly seen in the first three to five days post partum. The delirium usually immediately precedes or accompanies the physical manifestations but may appear several days after

the toxic state has been established. These patients present the physical picture[46, 47, 99] of an acute toxic state with fever, dryness of the skin or sweating, and rapid wiry pulse. Mentally, the most outstanding features are unclearness and confusion with disorientation, memory disorders, wandering of thought, derangements of perception, vivid auditory and visual hallucinations, disturbances of comprehension, and even states of stupor. The emotional state is variable, some patients being fearful while others are apathetic. In some, the emotional changes are at times suggestive of a manic or depressive reaction, while others show occasional bizarre reactions of a schizophrenic or persecutory nature. While in this confused state, these patients usually discuss their personal problems either openly or in a symbolic manner.

During the acute psychosis, these patients present a difficult problem in management because of their excitement and overactivity. The fear induced by terrifying hallucinations and the state of disorientation may lead to efforts to escape their persecutors and tragic accidents and suicides have occurred when adequate supervision was not available. Practically all recover their previous mental status without psychotic residuals, but the duration of the illness is extremely variable. Some recover their mental health as soon as the toxic factor is removed; others remain confused for a few days or weeks, while a small percentage continue in a confused state for months before re-establishing mental equilibrium.

CASE 4.—A married woman, aged 21 years, a primipara at term, was admitted to the obstetrical ward because of recurrent vaginal bleeding. She soon went into labor and a healthy child was delivered by episiotomy and the low application of forceps. Examination of the placenta revealed old blood clots, showing that premature separation had occurred. Twenty-four hours after delivery she had a severe chill and the temperature was elevated to 104.5° F. and fluctuated about this level for the next nine days. The patient complained of low abdominal pain, and muscular rigidity was noted in this area; the lochial discharge became foul and profuse. As the pelvic inflammation subsided, it was possible to palpate a mass in the lower right abdominal quadrant. Hemocytologic studies revealed a profound secondary anemia and leucopenia; intrauterine culture revealed gram-positive diplococci but repeated blood cultures were negative.

Coincidental with the onset of the fever, the patient became confused and bewildered. She was terrified at finding clusters of spiders on the wall, black cats surrounding her bed, and white cats on the bedspread. Men of monstrous appearance pulled the covers off her, while tiny golden men, four inches in height, with a spike growing out of the tops of their heads, ran and dove at her, imbedding their heads in her flesh. Thick, red lips appeared on the wall and poured out a torrent of obscenity and discussed her personal life. A huge woman had massive feet planted in opposite corners of the room and babies kept emerging from the giant labia, falling on the bed of the patient who tried to dodge them. At times she would inspect her hands minutely in a perplexed manner to ascertain if any small animalcules were present.

The confusion and clouding of consciousness varied considerably and periods of complete lucidity and logical thought alternated with episodes of unrestrained fear, screaming, and violent efforts to defend herself or escape from her persecutors. At no time did she express any organized ideas of persecution. She had no idea of why these things were happening and could think of no one who would wish to harm her.

The patient was given general supportive treatment, oxytocics, blood transfusions, and sedation. The pelvic infection rapidly responded to treatment, and there was a simultaneous improvement in the mental condition. At the end of ten days, she was mentally clear and had insight into her previous condition. Discussions revealed

that she was an average middle-class woman who was happy and satisfied with her life and had no outstanding psychologic problems. She was discharged in excellent condition and has remained well.

2. *The Nontoxic Deliria.*—These are variously known in the psychiatric literature[46, 47, 49, 50, 96] as "amentia syndrome," "symptomatic psychoses," "exhaustion psychoses," "confusional insanity," and "symptomatic confused states." The patients displaying this syndrome often have a history of psychopathic heredity, pre-existing mental instability, and exaggerated psychologic responses to slight toxicity or exhaustion. Although it is generally assumed that this reaction pattern is in response to anemia, severe exhaustion, or toxic-infectious factors, this belief cannot be substantiated in the majority of cases. Usually the history reveals a normal, uncomplicated delivery and careful examination fails to demonstrate physical depletion or intoxication. In many of these patients the evidence of toxicity or exhaustion is so negligible that the diagnosis rests entirely on the psychiatric findings.

This syndrome appears almost exclusively in the post-partum period and may begin in two different ways, but the subsequent reaction pattern is the same in both instances. One group of patients experience the above-mentioned acute toxic delirium which continues in an attenuated form long after the precipitating complication has disappeared. Sir James Simpson pithily described this sequence, "The morbid clockwork runs on long after the key that wound the spring is withdrawn." The second group usually have a gradual onset two or three weeks after delivery. The clinical picture of the syndrome suggests a diluted delirium. Again, the outstanding manifestation is confusion and clouding of consciousness, the patient behaving in a dazed and bewildered manner. At first, she seems to be somewhat toxic and physically ill but little or no confirmatory evidence can be adduced. Later, this aspect of physical illness disappears, unless reinforced by nutritional disturbances and dehydration, and only the mental manifestations remain. The bewildered patient acts as though she were in a dream from which she cannot awaken. Usually the emotional state is one of perplexed apathy but episodes of fear and panic occur in reaction to threatening imaginary voices and terrifying delusions. Mental processes are slowed and confused, the patient speaking infrequently in a flat, halting voice. Complete disorientation often occurs. The patient's personal conflicts gain expression in symbolic thought and behavior resembling the mental processes of a dream. In some cases marked manic-depressive or schizophrenic trends may occur and occasionally one of these types may crystallize out of the amorphous dream state.

The majority of patients are mentally ill for three to nine months but eventually complete recovery usually occurs. However, they are prone to recurrent episodes of delirium on the slightest provocation and always represent a poor psychologic risk for situations of stress. Those who do not regain mental health are usually incorrectly diagnosed cases of schizophrenia. Indeed, it is easy to undervalue the manic-depressive or schizophrenic symptoms in these patients and occasionally they are later observed in an unequivocal attack of one of these disorders. The patient who shows strong trend reactions in a delirium is a poor mental risk for future pregnancies.

(To be concluded in the February issue of the JOURNAL)

Editorial

Maternal Pulmonary Embolism by Amniotic Fluid

IN CONSIDERING the problem of inexplicable maternal death occurring during or shortly following labor, clinicians will welcome a new point of view provided by the pathologists Steiner and Lushbaugh,* of the University of Chicago. As a result of their study of eight women, these authors have described a new obstetric syndrome which they believe to be responsible for most, if not all, deaths heretofore variously ascribed to obstetric shock, idiopathic post-partum uterine atony with hemorrhage, acute pulmonary edema of pregnancy, and other obscure conditions. Clinically, the syndrome is characterized by shock. Predisposing factors are uterine tetany, over-size baby, multiparity and advancing age of the mother. The essential pathologic lesion is a widespread embolism of the small pulmonary arteries by amniotic debris, vernix caseosa and meconium. The clinical and pathologic picture can be reproduced in rabbits and dogs by the intravenous injection of the particulate matter found in human amniotic fluid. The frequency of fatal cases in obstetric practice is estimated to be about 1 in 8,000 confinements. The condition is believed by the authors to be the commonest cause of death during labor or in the first ten hours of the puerperium.

A queston of major importance for clinicians in this interesting and stimulating new thesis is whether pulmonary embolism by amniotic fluid is capable, per se, of causing obstetric shock. The authors' animal experiments provide the only direct evidence on this point, since the data of their human case material show that every patient suffering from embolism also had post-partum hemorrhage or some other abnormality which might conceivably have accounted for her shock. Inasmuch as evidence of animal experiments in a question of this kind can be accepted only with reservations, it is earnestly to be hoped that further investigation may settle it. For, as the authors themselves state, the diagnosis of the embolism can be made only by the presence of shock, and by the absence of any adequate explanation for it; physical signs in the chest are minimal or absent. Because post-partum hemorrhage or other potential causes of shock are, however, uniformly present, considerable clinical acumen must be needed in making the diagnosis, and even more in withholding the giving of blood, which the authors feel is contraindicated in the treatment of this syndrome. Unless the primary question can be answered, therefore, there is danger lest an uncritical ac-

*Steiner, P. E., and Lushbaugh, C. C.: J. A. M. A. **117**: 1245 and 1340, 1941.

ceptance of the new thesis may lead to the loss of lives that might otherwise be saved. Such premature acceptance, moreover, is likely to be encouraged rather than otherwise by the authors' statement that their syndrome is probably the commonest cause of death from obstetric shock. Such a conclusion can hardly be correct unless it is also true that a majority of such deaths occur among women bearing extraordinarily large fetuses. At least half of the fetuses in the authors' cases were of very unusual size.

Whether the new type of embolism be eventually confirmed as a major cause of obstetric shock or not, however, is less pertinent for the moment than the fact that Steiner and Lushbaugh have made a contribution for which all clinicians will be grateful. Not only are their ideas on maternal shock as stimulating as any that have been advanced in recent years, but their studies have been conducted with unusual care and completeness. As such, they deserve the earnest attention and study of all obstetricians.

CARL BACHMAN, M.D.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Obstetrics and Gynecology

Obstetric Analgesia, Twilight Sleep, the Barbiturates in Labor[1] is a large, elaborately assembled monograph by Juan Leon containing numerous colored charts. After detailing the foreign and Argentine literature, he discusses the pharmacology of the barbiturates. The study itself utilizes pentobarbital sodium (nembutal) alone (80 cases), with scopolamine (40 cases), with paraldehyde (40 cases), and with chloral (50 cases).

The action on the child was noticeable but less than that observed with opiates. Fetal mortality was nil. Complete analgesia and amnesia was 39.6 per cent, relative 49 per cent, failure 9.5 per cent. Maternal mortality none. This is a clear-cut, scientific study of childbirth in all its phases, presented in a fascinating way.

R. T. FRANK.

This well-known standard textbook for nurses, *Obstetrics for Nurses*[2] by DeLee and Carmon, appears in its twelfth edition. The authors state that they have noted the advances in the science and practice of obstetrics and have included in this edition a simplification of the treatment of the puerperium as well as the more complex and exacting system of prenatal care now in use. There is much new material for the public health nurse and the subject of cross-infection in hospitals has received due consideration.

An innovation is the inclusion of a teaching outline on obstetrics for nurses, in thirty lessons. The outline and suggestions for the lectures should be helpful to the many physicians who are concerned in nurses' education.

PHILIP F. WILLIAMS.

In *Die Tägliche Gynäkologische Sprechstunde*[3] by Rodecurt, we have an interesting discussion of the common lesions of the pelvic organs, and their abnormal physiology, which forms the bulk of the clinical practice of gynecology. He begins with a chapter on the relationship and influence of the heart, gastrointestinal, renal, and other systems on pelvic pathology and abnormal physiology. The author regards the *Trichomonas vaginalis* as an etiologic factor in 88 per cent of all cases of leucorrhea; mechanical cleansing of the vagina is favored as the best treatment.

[1] **Analgesia Obstetrica, el sueno Crepuscular Barbiturico en el Parto.** By Juan Leon, Professor Adjunto de Clinica Obstetrica de la Faculdad de Ciencias Medicas de Buenos Aires, etc. 574 pages, 169 illustrations. El Ateneo, Buenos Aires, 1941.

[2] **Obstetrics for Nurses.** By Joseph B. DeLee, M.D., Professor of Obstetrics and Gynecology, Emeritus, University of Chicago, etc., and Mabel C. Carmon, R.N., Chief Supervisor and Instructor in the Birth Rooms, Chicago Lying-in Hospital, etc. Twelfth edition, revised. 291 figures, 651 pages. W. B. Saunders Company, Philadelphia, 1941.

[3] **Die Taegliche Gynaekologische Sprechstunde.** Von Dr. M. Rodecurt, Frauenarzt. 308 Seiten, 3 Abbildungen. Georg Thieme, Leipzig, 1941.

Other features of trichomonas infestations, its ascent into the uterus and peritoneal cavity, such infestations in men and in very young children are described. The author makes no mention of the use of the sulfanilamide group in the treatment of gonorrhea in women. There is an excellent presentation of the pituitary-ovarian-uterine relationship in a chapter on abnormal bleeding; and this cycle is further elaborated in the chapter on insufficiencies of hormones. Presumably, the many proprietary drugs mentioned in this chapter are estrogen preparations. Rodecurt says in a chapter on sterility that this condition in Germany is responsible for a 100,000 birth loss each year. There is a chapter discussing the neuralgic-neuritic-vegetative symptom complex, in which a multitude of remedies are suggested. There is a short and rather unusual chapter on the cosmetic aspect of gynecology. The book ends with a discussion of dietetics.

PHILIP F. WILLIAMS.

Endocrinology

Hoskins' *Endocrinology*[4] is a well-written survey of the entire field of endocrinology designed to interest the biologist, psychologist, premedical student, the physician who desires a "non-too-technical" hormonology, as well as the intelligent general reader. Such a task is not easy. The author has not oversimplified, nor resorted to the blatant "journalese" to which some writers have descended.

In the main his exposition is clear-cut, well arranged, and really informative. From the view point of the general reader, it may prove too detailed and confusing; from that of the biologist, too sketchy, and yet its appeal will include a large number of readers.

A huge amount of well-documented information, covering the entire field, will be found in these pages, including some of the newest investigations. The personal views of the author, naturally, as they should, tinge the presentation in many ways. Here his wide knowledge of the literature and his personal experience in the laboratory enable him to evaluate the important high lights justly.

In the introduction he turneth away wrath by stating "In assembling the data, . . . only a part of the obligations thus incurred are indicated in the text and in the literature lists." Yet such names as that of Marine in connection with the mass prevention of colloid goiter and that of Zondek in the clarification of the function of the adenohypophysis, should not have been omitted. Numerous and well chosen illustrations illuminate the text.

R. T. FRANK.

The *Archives of the Clinic and Institute of Endocrinology at Montevideo*[5] have been published in two large fascicles, the work extending from 1937 to 1940. The reviewer's work was much facilitated by the summaries in French, English or German which conclude many of the articles, but many of the subjects were of sufficient interest and importance to warrant his reading them in the original Spanish. An introduction by Fournier, the director of the Institute, gives a background and history of endocrinology. The subject matter covered in these Archives is huge and contained in more than sixty-five articles. Some of these have appeared in the South American medical journals; others are reported here for the first time.

[4] **Endocrinology.** By R. G. Hoskins, Ph.D., M.D., Director of Research, the Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School. Illustrated, 388 pages. W. W. Norton & Company, New York, 1941.

[5] **Archivos de la Clinica e Instituto de Endocrinologia.** Director, Professor J. C. Mussio Fournier. Tomo I, Fasc. 1. and 2. (1937-1940). Imprenta "Rosgal." Montevideo, Calla Cerro Largo, 1941.

Many articles deal with changes in bone and other portions of the body, due to hypo-and hyperthyroidism, among which I mention the resistance to therapy, eventually developing in the pitting edema of myxedema, as well as the anginas associated with thyroid disturbances. Attention is called to the so-called pseudo-Froehlich syndrome which is merely of transient nature. Many articles deal strictly with the laboratory phases of endocrinology, including bio-assay methods for the gonadotropic factors, many experiments on the various sex hormones and the adrenal hormones, as well as changes in the technique of bio-assay and of the male sex hormone. Clinically, attention is drawn to the increase in metabolism frequently noted in the menopause. An important article deals with the adjuvant action of estrogens in the treatment of menopausal diabetics. A report on the activities of the clinic shows that nearly four thousand patients were treated in the course of three years at the Institute. All in all, this is a very important contribution to endocrinology.

R. T. FRANK.

Office Endocrinology[6] by Robert B. Greenblatt is a small brochure, covering a number of particular procedures for office methods of treatment which the general practitioner might want to perform. The presentation is somewhat haphazard, apparently not following any definite arrangement. Such procedures as vaginal smears, suction curettage, and the application of the Friedman pregnancy test are well described. Just why the short chapter on ''Embryologic and Histologic Considerations of the Ovary'' and ''The Nature of the So-Called Syncytioma'' are included, is not apparent. The author appears to consider that the treatment of bleeding from the myomatous uterus should be controlled by testosterone, with which not all will agree.

R. T. FRANK.

Miscellaneous

Abdominal Surgery of Infancy and Childhood,[7] by Ladd and Gross, represents a portrayal of the surgical experiences accumulated by the surgical staff of the Boston Childrens Hospital over a period of twenty-five years. The original stimulus from which this book has been developed was the extraordinarily high mortality rate in children as compared with adults. This, the authors believe, is due to certain types of infection and to the many congenital abnormalities which are seldom encountered in later life. As one might expect, a great deal of the text refers to congenital malformations or dysfunctions and to various forms of herniation. Various lesions of the genital tract of both girl and boy babies have been discussed at some length. In discussing neoplasms of the ovary, Ladd describes five cases of malignancy in the eight instances encountered in his institution. X-ray irradiation, he states, should not be used following malignancy in ovarian neoplasm in children. The inclusion of a discussion of vaginitis in a text on abdominal pregnancy seems somewhat irrelevant.

The book is amply illustrated. The pathology, symptoms, signs, and differential diagnosis are thoroughly interpreted, and the technique is set up in detail. One feels that this volume should be of value to those who must diagnose and treat children's diseases.

PHILIP F. WILLIAMS.

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[6]**Office Endocrinology.** By Robert B. Greenblatt, B.A., M.D., C.M., Professor of Experimental Medicine, University of Georgia, School of Medicine. Published under the auspices of the University of Georgia, School of Medicine. Walton Printing Co., Augusta, Georgia, 1941.

[7]**Abdominal Surgery of Infancy and Childhood.** By William E. Ladd, Professor of Child Surgery at Harvard Medical School, etc., and Robert E. Gross, Associate in Surgery, Harvard Medical School, etc. 268 illustrations, 455 pages. W. B. Saunders Company, Philadelphia, 1941.

The authors of this book, *The Premature Infant*,[8] have had some twenty years of experience in the care and study of premature infants at the Premature Station of Sarah Morris Hospital, Chicago. Their contributions to this field of infant care are of considerable importance, when one considers that about half of the deaths of infants during the first month of life in the state of Illinois are reported as being caused by prematurity. The value of this book lies in its practical approach to the medical and nursing care of the premature infant. The equipment necessary for the proper care of these infants either in the hospital or in the home, or for transportation from home to hospital is described. Since, as the authors stress, adequate nursing personnel and care are of major importance for the survival of the premature infant, the greatest value of this book can be found in its careful and detailed description of the nursing technique and the daily routine employed at the Sarah Morris Hospital.

Where adequate care for the premature infant is made available to the entire population, a considerable saving of lives will result. A city-wide plan, with the Cook County and the Sarah Morris Hospitals as centers, has been in effect in Chicago since 1934. Since that year the infant mortality per 1000 under one year of age has dropped from 47.7 in 1934 to 28.8 in 1940. During the same time, the premature mortality has dropped from 42.6 per cent in 1934 to 20.8 per cent in 1940.

SOL LONDE.

This new volume, *Operative Surgery*,[9] is a treatise on the surgical treatment of abdominal diseases, to which there has been added a separate discussion of such related subjects as anesthesia, pre- and postoperative treatment, surgical technique, and blood transfusions. The material has been contributed by thirty-four authors, all eminent in their particular fields, and edited by F. W. Bancroft.

The subject is divided into twenty sections, of which fifteen deal directly with abdominal surgery. The first section, a general discussion of the various types of anesthesia as well as pre-anesthetic medication, has been prepared by six authors. Blalock's section on Pre- and Post-Operative Therapy discusses not only actual technical details, but brings out the methods of handling abnormal physiology due to either general conditions or local disturbances. This section should be of value to gynecologists as well as to the abdominal surgeons. In discussing blood transfusions, Stetson describes the methods of preserving blood as well as the various blood substitutes. This section is of considerable interest because of the development of these methods in surgery of the present war. Stevenson and Reid have made an outstanding contribution on the fundamental principles of surgical technique. For the young or occasional operator this section should be of great help. The various sections on the surgery of abdominal disease leaves no room for criticism. In addition to the special section on anesthesia and pre- and postoperative treatment, practically all specific sections contain the individual ideas of the various authors with regard to anesthesia and preoperative care. Under surgery of the spleen, Maes and Rives have discussed at length the physiology and disorders of function in order that the surgeon may have at his command the available knowledge regarding the conditions for which surgery of this organ may be indicated. The book closes with a section on Nutrition in Abdominal Conditions by Anthony Bassler. This is an excellent section.

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[8] **The Premature Infant.** Its Medical and Nursing Care. By Julius H. Hess, Professor and Head of Department of Pediatrics, University of Illinois College of Medicine, etc., and Evelyn C. Lundeen, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital, Chicago. 309 pages, 74 illustrations. J. B. Lippincott Company, Philadelphia, 1941.

[9] **Operative Surgery, Including Anesthesia, Pre- and Postoperative Treatment, Surgical Technic, Blood Transfusion and Abdominal Surgery.** Edited by Frederic W. Bancroft, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, etc. 1102 pages, illustrated. D. Appleton-Century Co., New York, 1941.

This book is a splendid contribution. Because of the relationship between pelvic and abdominal lesions in their general aspects and not infrequent association, it might seem that it was almost a "must" text for the library of the gynecologic surgeon.

PHILIP F. WILLIAMS.

Ellinger presents the subject of *The Biologic Fundamentals of Radiation Therapy*[10] in a well-balanced volume. The expansion of the therapeutic use of radiation should make this presentation of value not only to radiologists but to physicists and practitioners. Following an excellent consideration of the physical and biologic properties of radiation, the author refers to the action of radium on the various tissues and systems of the body.

In the second part of the book, he describes the corpuscular rays and in the third part the ultraviolet light, concluding with a discussion on radiation, biology, and therapy. His closing chapter is one of particular value, for here he discusses radiation injuries and their prevention.

Ellinger describes the effects of radiation upon the endocrine glands and makes an important point in that a fundamental difference exists between the effect on healthy and diseased organs. He states further that radiosensitivity and anatomic changes do not always go hand in hand. He regards the healthy pituitary as radioresistant to a very large degree. The pathologic pituitary, he states, reacts well to irradiation. Discussing the effects of radiation upon the ovary, he brings out very clearly reversible and irreversible reactions. There is an interesting description of the effects of radiation upon the course of pregnancy and the fetus, and this topic is brought up again in another chapter on the "Effects on the Progeny of Radiation." Further in the text he discusses the physics of ultraviolet light, and other light rays, and the treatment of diseased organs by light. The bibliography includes 1,110 items and must be regarded as unusually comprehensive. This is a very full and interesting presentation of the subject.

PHILIP F. WILLIAMS.

Biological Symposia,[11] edited by Jaques Cattell, in its Volume III, presents a source book of information on "Muscle." The introductory by the editor of this volume, Wallace O. Fenn, draws attention to the great interest presented by muscle for physiological, chemical, and physical research. The fifteen articles cover many phases of the subject, from study of function of a single fiber, through action potentials, innervation, conduction, metabolism, and diseases of muscles. The contributions are by authors well known in this field of research.

R. T. FRANK.

These two volumes conclude the system of *The Therapeutics of Internal Diseases*[12] edited by George Blumer. In Volume IV, "The Alimentary Tract and Its Appendages, The Genito-Urinary Tract, Hematic and Locomotor Systems," are discussed by fourteen authors. This is a comprehensive presentation, bringing out all

[10]**Radiation Therapy. Its Biologic Fundamentals.** By Friedrich Ellinger, M.D., Research Fellow, Radiotherapy Department, Montefiore Hospital, New York City. 79 figures in text, 360 pages. Nordemann Publishing Company, Inc., New York, 1941.

[11]**Biological Symposia. Vol. III. Muscle.** Edited by Wallace O. Fenn, Professor of Physiology, School of Medicine, University of Rochester, N. Y. Illustrated, 370 pages. The Jaques Cattell Press, Lancaster, Pa., 1941.

[12]**The Therapeutics of Internal Diseases.** Supervising Editor: George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., Associate Editor: Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. Volume IV, 791 pages, and Volume V, 765 pages, both illustrated. D. Appleton-Century Co., New York, 1941.

the modern advances in these conditions, with excursions into such varied lines of therapy as vitamins, physiotherapy and psychotherapy.

The chapter on the "Treatment of the Diseases of the Rectum and Anus" will be of particular interest to the gynecologists and obstetricians, as such lesions are very frequently called to their attention. The same might be said for the diseases of the genitourinary tract. There is an excellent section on sterility in the male. Here, the author has been cautious in his recommendations of hormones or their synthetic substitutes, and stresses the need for avoiding an antihormone response.

Musselman of New Haven has written an excellent chapter on "The Nonoperative Treatment of Gynecologic Diseases," particularly the menopause. Especially valuable for the general practitioner is the discussion regarding the indication for operative intervention in pelvic disease. The quickening interest in obstetric circles regarding the classification of the hypertensive complex in late pregnancy should make a study of Mosenthal's section on Nephritis and Hypertension worth while.

The fifth and final volume represents the contributions of ten authors. Turner discusses the "Diseases of the Endocrine Glands." Valuable, from a practical point of view, is the list of the commercial preparations and their equivalent values in estrogen, progesterone, etc. He, too, cautions regarding antibody formation in the use of these preparations. It is not without interest that he omits all mention of x-ray therapy in hypofunctional states.

The Smiths offer an extremely well-developed and modern concept of the use of vitamins in therapy in medical practice. Particularly good in this section is the discussion of physiology of the various vitamins and of the subclinical deficiencies.

PHILIP F. WILLIAMS.

The enlarged scope of health education in many communities has created a demand for a book on unified health education programs.

This manual, *Community Organization for Health Education,*[13] is a committee report of the American Public Health Association to the Public Health Education Section and the Health Officers Section. It discusses the need of community organization for health education, and advises a cooperative effort on the part of the health departments, school systems and private agencies for such work. Procedures are given which might be adopted by different combinations of agencies, and examples are shown how various communities and cities have followed the recommendations. While there are differences in the basic plans and functions of the various agencies, this manual brings out the facts and shows how the difficulties in the organization of almost any community to achieve the maximum health may be overcome.

PHILIP F. WILLIAMS.

The 1940 volume of the New York Academy of Medicine on medical lectures to the laity, *March of Medicine,*[14] has as much interest for this reader as any of its predecessors. Dr. Solley in the Introduction tells of the great interest today of the general public in scientific matters and explains the necessity for interpretation of the fragmentary facts reported in the press. Myerson discusses the "Inheritance of Mental Disease." It is interesting to note his negative opinions on sterilization employed to counteract the lines of heredity in mental conditions. In his essay, "Ascent from Bedlam," Hutchings describes present-day care of mental disease. Perrin Long gives a fine story of the discovery and clinical application of the

[13] **Community Organization for Health Education.** A Committee Report of the American Public Health Association. 120 pages. The Technology Press, Cambridge, Mass., 1941.

[14] **The March of Medicine.** New York Academy of Medicine Lectures to the Laity, 1940. Columbia University Press, New York, 1941.

sulfanilamide group. Long states "never before has such progress been made in the treatment of infectious disease as we have witnessed in the last five years." Resnikoff in an easy style describes the blood dyscrasias, mechanisms of blood coagulation, and the fascinating story of transfusion. Thomas Rivers tells most entertainingly the story of viruses, yellow fever, influenza, and other virus diseases. The volume will probably prove as beguiling to the physician as to the laity for whom it was originally intended.

PHILIP F. WILLIAMS.

Dorland's *The American Illustrated Medical Dictionary* appears in its nineteenth edition.[15] This well-known, standard volume contains more than two thousand additional words pertaining mainly to endocrinology, physical therapy, biochemistry, psychiatry, drugs, surgery, signs and symptoms of diseases. In spite of continued accretion, it still remains within the compass of convenient desk size.

R. T. FRANK.

Tuberculosis and Psychoses[16] with especial reference to the etiology of "discordant psychoses" is a monograph by Melgar in which he deals with the association of dementia praecox and tuberculous infection. A most detailed presentation of the world literature covering modern concepts on the etiology of the disease, serology and bacteriology is given. A large number of case histories are abstracted. The treatment of thirty-six patients with "Solganal B," a proprietary gold salt, resulting in 22 per cent of remissions, is detailed.

R. T. FRANK.

Complete Weight Reducer[17] is a volume arranged in dictionary form, covering a large number of topics which might be useful for reference, particularly by the laity, and save them from being unnecessarily exploited by charlatans who abound in the field.

R. T. FRANK.

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[15]**The American Illustrated Medical Dictionary.** By W. A. Newman Dorland, M.D., F.A.C.S. Nineteenth edition, revised and enlarged, with 914 illustrations, including 269 portraits. 1647 pages. W. B. Saunders Company, Philadelphia, 1941.

[16]**Tuberculosis y Psicopatias.** By Dr. Ramon Melgar. 266 pages. Talleres Graficos "Gasperini," Buenos Aires.

[17]**Complete Weight Reducer.** By C. J. Gerling. Harvest House, New York, 1941.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Sterility

Williams, W. W.: The Germ Plasm Factor of Sterility, Urol. & Cutan. Rev. **44**: 582, 1940.

In the opinion of the author many of the obscure cases of sterility are evidently due to germ plasm disease, and this presents considerable difficulty, both in the matter of recognition of definite pathology, and of possible underlying etiologic factors.

In the male, the examination of spermatozoa furnishes a rather direct method of appraising spermatic health. It indicates the performance probabilities of sperm populations but not necessarily the potentialities of individual germinal cells which deviate markedly from the pattern of the rest of the population.

In the female, the appraisal of germ plasm disease is less direct. Endometrial biopsies indicate whether or not an ovum has developed sufficiently to cause maturation of the follicle and subsequent lutein formation. It indicates the activity of the secretions elaborated by the follicle and the corpus luteum, but tells nothing of the fitness of the mature ovum for fertilization.

Often little or no attention is given to spermatic defects, the attempt being made to gauge spermatic health by motility reactions alone. In the author's experience the most dependable evidence of significant spermatic disease is usually derived from a study of stained semen smears. Normal fertile men rarely produce over 20 to 30 per cent abnormal spermatozoa, whereas with infertile men the presence of over 40 per cent structurally abnormal cells is a common feature. Pathologic spermatozoa are often highly motile. It happens that most males who are sterile because of germ plasm disease will deliver in each ejaculate (aside from the abnormal cells) millions of normal-appearing, active spermatozoa. Experience has shown that the normal-appearing cells occurring in markedly pathologic sperm populations are commonly incapable of fertilizing an ovum, in spite of their normal appearance and behavior.

A woman who has anovulatory menses is likely to be sterile whether the anovulation is or is not a constant factor. There is no more justification for assuming that ova are normal because they develop sufficiently to cause the elaboration of estrin, progesterone and the concomitant endometrial changes, than to assume that all normal-behaving spermatozoa are always functionally capable of impregnating an ovum.

Unless woman is more efficient than animals in the development of healthy ova, and unless there exists in woman a marked difference in the relationship of normal ovogenesis to the estrual cycle and the concomitant changes, then we must assume that a much larger ratio than commonly supposed of so-called functional sterility, is actually the direct result of abnormal female germ plasm. Add to this the sterility of male germ plasm origin, and a problem of considerable magnitude is presented. Lesser abnormalities of the ovum and sperm may be difficult or impossible to demonstrate by any type of known laboratory test. The effect of the union of two such cells with only slightly diminished vitality may, however, be clinically as important as an outstanding defect of a single gamete.

Indications of germ plasm pathology are frequently observed in spontaneous abortions where blighting of the fertilized ovum and abnormalities of the fetus are common features. It is a common clinical observation in spontaneous abortions that the fetus cannot be found. Spontaneous abortions, as anovulatory menses, are more common with women of low fertility, those with irregular menses, and those approaching the menopause.

J. P. GREENHILL.

McClellan, R. H.: Human Sterility. Analysis of a Series of 400 Specimens of Spermatic Fluid, Pennsylvania M. J. **43**: 1582, 1940.

The group study of sterility is the most logical approach and it should be systematic and complete, including both partners. A simplified but adequate technique for the laboratory examination of semen is outlined by the author.

A properly obtained specimen in relation to continence and method of obtaining it is of significant importance. It is emphasized that the finding of mere motility in the ejaculation does not always mean a normal specimen nor a potent male. Motility lasting sufficient time for the transport of the spermatozoa to the ovum is necessary for fertilization of the ovum, and in an adequate study of semen the duration of motility and activity of the spermatozoa should be investigated.

A study of the morphology by differential stain and count is a necessary part of an adequate assay of the semen, as more than 25 to 30 per cent of abnormal forms indicate at least temporary sterility for the male. A single though complete examination may be misleading, and it is urged that repeated examinations of specimens, obtained under as nearly ideal conditions as possible, be made. In an analysis of 400 consecutive specimens of semen from partners in sterile marriages, it was found that a large portion of the males (54 per cent) have abnormal semen and therefore, are to this extent responsible for the sterility.

J. P. GREENHILL.

Pryde, John: A Contribution to the Study of Human Fertility, Brit. M. J. **1**: 12, 1941.

The author is of the opinion that there exists within the human intermenstrual cycle a limited period of fertility. To support this view he gives data abstracted from complete records of sexual activity kept by two pairs of young married partners. The first pair had 126 and the second 450 uncontracepted acts throughout 33 and 61 consecutive intermenstrual cycles respectively. These were distributed so that none fell between the tenth and thirteenth day of the cycles. No pregnancies occurred. Following this, pregnancy immediately resulted in both cases when the first uncontracepted acts occurred within the tenth to the thirteenth day of the cycle. The author believes that a general investigation along such lines, with couples who would keep accurate day to day records, would substantiate his findings of the existence of a limited period of fertility in the intermenstrual period.

FRED L. ADAIR AND W. H. PHILLIPS.

Lamar, J. K., Shettles, L. B., and Delfs, Eleanor: Cyclic Penetrability of Human Cervical Mucus to Spermatozoa in Vitro, Am. J. Physiology **129**: 234, 1940.

A new method of studying penetration of cervical mucus by spermatozoa in vitro includes the use of microtubes and barrier-marker bubble. This method is considered better than slide-cover glass preparations because it prevents undiscoverable mechanical mixing of mucus and semen and drying of the preparation, and because it can be used to study penetration quantitatively and also to study longevity of the spermatozoa in the mucus.

Results of this method confirmed the "in vivo and in vitro" findings of Seguy and Vimea, namely, that there is a cyclic production of a glairy, translucent

cervical mucus at about midcycle, which renders the cervix temporarily penetrable for spermatozoa. Roughly, the spread of this phase in this study was from day 9 through 19, but for any one cycle this period may be restricted to about four days. Indications are that menstrual discharge is penetrable by spermatozoa, but the mucus of the phase between menstruation and the midcycle is relatively impenetrable, and that of the phase between midcycle and the subsequent menstruation is impenetrable.

Correlated with the midcycle peak in penetrability is the peak in freedom from leucocytes, the peak in pH (except during the menstrual flow), the peak in the amount of mucus secreted, and the height of conditions favoring greatest longevity of spermatozoa in the mucus. It may well be that the actual viscosity of the mucus encountered by spermatozoa is lowest at the midcycle. It is suggested that both low pH and large number of cells in the "secretory phase" of the menstrual cycle may be caused, at least in part, by the low rate of secretion of the mucus.

An investigation of the cervical mucus over the cycle, by the "in vitro" method, is suggested in cases of otherwise unexplained sterility. A field of usefulness for artificial insemination may be developed in sterilities due to a persistent impenetrable cervical mucus.

J. P. GREENHILL.

Brunner, E.K.: An Experiment in Temporary Immunization Against Pregnancy, Human Fertility **6**: 10, 1941.

The author used a phospholipid antigen prepared from sperm masses obtained from young bulls. The antigen, and the antigen plus cevitamic acid were injected into groups of female rabbits. None refused to copulate and no immunity to pregnancy resulted.

R. J. WEISSMAN.

Brown, R. L., and Gamble, C. J.: Comparative Spermicidal Powers of 15 Commercial Contraceptives, Human Fertility **6**: 1, 1941.

The authors describe their technique of determining the spermicidal time of jelly type contraceptives in vitro. Thirteen of the marketed products show variations in spermicidal time from 2 to 348 minutes.

R. J. WEISSMAN.

White, M. D.: The Effect of Follicular Hormone on Non-Patent Fallopian Tubes, Brit. M. J. **1**: 342, 1940.

White gave courses of five estradiol benzoate injections of 50,000 I.B.U. each at five-day intervals to 9 patients whose Fallopian tubes were nonpatent and 4 patients in whom the tubes were only slightly patent.

Five days after completion of the injections, the tubes were patent in 5 of the 9 women showing previous nonpatency, 4 having good tubal contractions. Of these, one of the women was five months pregnant at the time of the report and two others had had their first menstrual periods delayed two weeks following the treatment which the author interprets as early miscarriages.

Of the 4 patients showing patency only at high pressures, 3 became patent at lower pressures and one of these now has good tubal contractions.

The author reiterates Clauberg's theory that the tubal hyperemia produced by estrin stimulation softens the tubes so that where fine adhesions are present which obliterate the lumen, further instillations of lipiodal or carbon dioxide insufflation may break them down and so effect patency.

FRED L. ADAIR AND RAY YOUNG.

Leinzinger, E.: Dangers and Injuries by Contrast Filling of the Uterus and Their Prevention, München. med. Wchnschr. **87**: 1023, 1940.

Leinzinger discusses the important advances made by hysterosalpingography in the diagnosis and therapy of sterility and warns that it should not be considered an entirely harmless and simple procedure. The injuries may be of a chemically toxic, mechanical, embolic, and inflammatory nature.

To prevent the accidents he urges that a careful history be taken and thorough physical examination be done, and to consider and decide carefully which therapeutic procedure and contrast medium should be used. Iodism, if an iodine preparation is used, should be kept in mind, the intrauterine pressure should not exceed 150 mm. Hg and latent adnexal infections be ruled out. Because of delayed reactions the patients should be under careful observation for several weeks, and he reports two patients in whom reactions followed three and seven weeks, respectively, after the procedure. By observing careful and necessary precautions, the number and type of complications can and should be as low as with any other diagnostic procedure.

C. E. PROSHEK.

Lorset, J.: Subsequent Investigation of Patients Operated on at the Oslo Clinic From 1928-1938 for Sterility Due to Tubal Occlusion, Acta. Obst. & Gynec. Scandinav. **20**: 344, 1940.

A series of 77 operations for closed tubes is reported. A follow-up revealed that nine and possibly 11 patients became pregnant following the operation. The author is uncertain about the two women who claimed to have had abortions. Among the nine definite pregnancies there were two ectopic gestations and seven full-term pregnancies.

Salpingography was performed after operation in 22 cases and the tubes were found to be patent in 17 instances. The author urges the use of salpingography following operation, and he has devised a special instrument for this purpose. He uses it during the operation and again on the fourth day, tenth day, and the twenty-eighth day after operation.

J. P. GREENHILL.

Vasciaveo, L.: Salpingotomy as Operative Treatment in Tubal Sterility, Ginecologia **18**: 472, 1940.

Vasciaveo reports from the Sterility Center at the University of Turin the follow-up upon 14 patients, who had been treated by salpingotomy for relief of their tubal sterility. The majority of these operations were performed as incidental gynecologic operations rather than primarily for the re-establishment of tubal patency. The plastic tubal surgery was usually secondary to hysteropexy in the treatment of retroversion or retroflexion, else to removal of unilateral residual adnexal inflammatory disease.

Eight of the patients submitted to uterograms. Six of these cases were demonstrated to have postoperative occlusion of the tubes while two cases had bilateral tubal patency following salpingotomy. The specific techniques of the successful operations were the Martin operation in one instance and the Philipps operation in the other.

CLAIR E. FOLSOME.

Clauberg, C.: Is There a Chance for Conservative Treatment of Sterility Caused by Occlusion of the Tubes? Wien. med. Wchnschr. **91**: 97, 1941.

The author answers the question in the positive. His method includes the following measures: First, a uterosalpingography with iodized oil is done. This procedure should be performed only by expert gynecologists. Second, the

patient is given a series of 12 to 25 short wave diathermy treatments to the deep pelvic tissue. The heat therapy is administered upon alternate days. Last, following the heat therapy courses, the patient is given an intramuscular injection of follicular hormone, 5 mg. every fifth day, for a total dosage of 25 to 30 mg. (250,000 to 300,000 mouse units). The author insists that the hormonal therapy must be given in the first half of the menstrual cycle.

Clauberg states that corollary to uterine growth the tubes show a correspondingly distinctive growth stimulation. He demonstrates, with roentgenographic evidence, that nonpatent tubes prior to the above-mentioned treatment, do become patent. In those patients with infantile-like uteri and demonstrable nonpatency of the tubes, he was able to relieve sterility with only the hormonal treatment. A series of halftone plates illustrate the author's evidence of convincing uterograms, taken before and after treatment.

CLAIR E. FOLSOME.

Amundsen, E.: Is Sterilization During the Puerperium Contraindicated? Acta. Obst. & Gynec. Scandinav. **20**: 295, 1940.

When sterilization must be performed, the best time for the operation is shortly following delivery. The advantages are that the patient is still in the hospital and that from a technical point of view the operation is simple. In a series of 150 sterilizations performed shortly after delivery at the Oslo Clinic, there were no deaths. Most of the operations were performed on the third day after delivery. Local anesthesia was used in practically all the cases, and the operation employed was resection of the tubal corners. In none of the cases was there any sign of infection or embolism, although thrombosis appeared in six cases. When a series of patients operated upon before 1932 is added to the present series, it is found that the incidence of thrombosis following sterilization is about 2 per cent. The author believes that this incidence could be considerably reduced by performing the operation on the first day after delivery.

In the discussion of this paper Sund mentioned that this method of sterilization was invented by Mannen thirteen years ago. Sund has performed about 300 such sterilizations and has not observed any deaths or any serious complications.

J. P. GREENHILL.

Dippel, A. Louis: Tubal Sterilization by the Madlener Method, Surg., Gynec. & Obst. **71**: 94, 1940.

Five clinical failures of tubal sterilization by the Madlener method were encountered in a series of 101 patients.

The areas of attempted sterilization were recovered at the time of a second sterilizing operation, from both tubes of 4 of these patients, and from 1 tube of the other. Each area was serially sectioned to ascertain the reason for failure.

One patient had a very early pregnancy at the time of the Madlener sterilization. In 2 instances considerable regeneration of the tubal lumen occurred, so that the ligating suture must have been improperly tied or placed or slipped off the knuckle. This error was bilateral in 1 case. In a fourth patient the tubal lumina were apparently completely obliterated but eventually an inferior lumen was re-established on one side by endosalpingosis. In the fifth instance, both tubal lumina were replaced by scar tissue but a small tuboperitoneal fistula apparently developed as a result of endosalpingosis on the medial side of the ligated knuckle of one tube.

The number of failures of tubal sterilization by this method should be reduced by more careful adherence to the technique as originally laid down by Madlener, although certain modifications do not seem to have increased the incidence of failures.

There were no maternal deaths associated with the 101 Madlener sterilization operations but in 369 women sterilized by other methods during the same years, 7 deaths occurred.

WILLIAM C. HENSKE.

Müller, F.: Pregnancy After Sterilization Operation, Zentralbl. f. Gynäk. **64:** 1010, 1940.

Müller cites an interesting case in which pregnancy occurred in a young woman thirteen months after partial excision of the tubes. On opening the abdomen again, the proximal ends of both tubes were found adherent to the fundus uteri. On the left the fimbriae were found adherent between the ovarian ligament and fundus. Methylene blue solution was injected through the cervix and appeared through a fistulous opening through the uterine wall under the region of adherence of the fimbria of the left tube. The fistula was excised and sectioned and showed a lining of tubal epithelium. The author concludes that remnants of tubal epithelium left on excision of the cornual portion of the tube proliferated and canalized the fistula.

R. J. WEISSMAN.

Correspondence

Adenocarcinoma of the Vulva

To the Editor:

In the August, 1941, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY there appeared an article by McDonald, Lovelady, and Waugh entitled "Adenocarcinoma of the Vulva," in which a total of thirty-two tumors are reported. The authors state: "Thirty of the neoplasms were papillary adenocarcinomas and because of this have been grouped together." We do not wish to take issue with the other two tumors. But the gross and microscopic descriptions and the photographs of these thirty so-called papillary adenocarcinomas are strikingly similar to the descriptions and photographs of what we called "Hidradenoma of the Vulva" in an article published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, 38: 509, 1939.

There can be no doubt that McDonald and his co-workers are describing the same neoplasms as we did. Although they mention hidradenomas of the vulva in their introductory work, they do not refer to the possible identity of hidradenoma with papillary adenocarcinoma. If they are the same type of newgrowth, as we believe them to be, it is important to determine whether they are benign or malignant so that they can be named suitably.

McDonald et al. discuss the question of malignancy:

"The problem can be brought up as to whether these papillary neoplasms represent true carcinoma or not. Because of their histologic character, it would seem better to refer to them as adenocarcinomas of a low grade of malignancy rather than simple adenomas. Metastatic growths were not found in any of the cases of papillary carcinoma. However, it would appear probable that if a sufficient number of these cases were studied, metastatic growths would be found eventually.

"From a practical standpoint it can be stated that because of the slow growth of the tumor and the slow tendency to metastasize, complete excision of the tumor together with a portion of the surrounding tissue is sufficient to effect a cure in these papillary carcinomas."

As one analyzes the various reasons given here by the writers for designating this newgrowth as malignant, one finds that the only actual evidence consists of "their histologic character." Fig. 1 of their report, they claim, shows that a "transition between the clear cells of the apocrine sweat glands and the carcinoma cells can be seen." We fail to recognize anything that we would call carcinoma. Our own cases, published and unpublished, closely resemble this histologic picture, but nowhere did we find any characteristics of malignancy.

Elsewhere, last sentence, page 305, they state that the capsule of the cyst occasionally was invaded by tumor cells. We found the same picture in our studies, but we felt that we were not dealing with invasion of the capsule but rather an artifact of sectioning. This is a common occurrence in papillary cystadenomas.

Although McDonald and his collaborators and ourselves have described the same histologic pictures, we have disagreed on the interpretation of this picture. We agree, however, on many other points: the tumors are slowly growing, they may exist for many years, metastases do not occur, mitoses are rare, the tumors are cured by simple excision, recurrences are not found. These qualities of tumors are widely accepted as the cardinal attributes of benignancy. The statement, that "if a sufficient number of these cases were studied, metastatic growths would be found eventually," sounds like rather belabored reasoning.

The classification of these obviously clinically benign tumors into Broders' Grade I and II adenocarcinoma seems to us inconsistent. The supposed usefulness of Broders' grading lies in the aid it is claimed to offer to the clinician in his therapeutic and prognostic attitude toward a given tumor. An effort to grade the degree of malignancy of apparently benign tumors is an attempt to attain the acme of confusion in terminology.

It is incumbent upon the pathologist to make the diagnosis of cancer only when he sees unmistakable evidence of malignancy. A tendency to straddle and play safe has undeniably resulted in innumerable unnecessary and risky radical operations. In the case of these tumors, there is no justification for applying the misleading term, papillary adenocarcinoma. It should be discarded. In spite of every effort we might make to convince the clinician or patient that a given adenocarcinoma is clinically benign, the appellation as carcinoma cannot fail to be disturbing. The term hidradenoma is histologically and clinically correct and preferable.

S. H. GRAY, M.D., *Director of Laboratories,*
St. Louis City Hospitals

St. Louis, Mo.
November 3, 1941.

Reply by Dr. McDonald

To the Editors:

I wish to thank you for referring Dr. S. H. Gray's comments to me in connection with an article entitled "Adenocarcinoma of the Vulva" written by Lovelady, Waugh, and myself and published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 42: 304, 1941.

Dr. Lovelady, Waugh, and myself feel that our position in regard to these neoplasms is stated in the paper and that very little further comment is necessary. After a thorough cytologic study, we expressed the opinion that these tumors were malignant, and we see no reason for changing our opinion at the present time. Since these tumors impressed us as being carcinomas, they were graded histologically, using Broders' criteria. Furthermore, two of our senior pathologists, Dr. A. C. Broders and Dr. H. E. Robertson, had reviewed the tumors in question and agreed with the conclusions reached.

A similar situation has prevailed in connection with the so-called carcinoid tumors of the ileum and appendix which in the past were considered by many to be benign. However, as more studies were completed, it was found that a sizable percentage of carcinoid tumors in the ileum metastasized, and present-day opinion seems to be swinging to the idea that all carcinoid tumors are slowly growing malignant neoplasms. Time alone will tell whether or not a similar situation will prevail in connection with what we have chosen to call papillary adenocarcinomas of the vulva.

JOHN R. MCDONALD, M.D.

Mayo Clinic,
Rochester, Minn.
November 14, 1941.

Items

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of $25.00 is required on registration, $10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

The general oral and pathologic examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, prior to the opening of the annual meeting of the American Medical Association in Atlantic City, on June 8, 1942.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942. It will greatly facilitate the work of the Board if applications are filed as far as possible in advance of the closing date for their receipt.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* W. C. Danforth, Evanston, Ill. *Secretary,* H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Next meeting, May, 1942, Sky Top, Pa.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* W. R. Cooke, Galveston, Texas. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at White Sulphur Springs, Va., September 9-11, 1942.

Central Association of Obstetricians and Gynecologists. *President,* John H. Moore, Grand Forks, S. D. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Next meeting, Des Moines, Ia., October, 1942.

South Atlantic Association of Obstetricians and Gynecologists. *President,* R. A. Bartholomew, Atlanta, Ga. *Secretary,* Robert A. Ross, Durham, N. C. Next meeting, February 6-7, 1942, Atlanta, Ga.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* W. T. Dannreuther. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.

New York Obstetrical Society. *President,* H. J. Stander. *Secretary,* Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* T. L. Montgomery. *Secretary,* John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Charles E. Galloway. *Secretary,* James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* George G. Cochran. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. *President,* Abraham Samuels, *Secretary-Treasurer,* Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* E. W. Enz. *Secretary,* Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* Thomas Evans, Jr. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. *President,* John Rock. *Secretary,* Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

New England Obstetrical and Gynecological Society. *President,* Frederick L. Good. *Secretary,* R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. *President,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, San Francisco, Calif., November, 1942.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

Washington Gynecological Society. *President,* W. J. Stanton. *Secretary,* L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* E. L. Zander. *Secretary,* Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* E. Lee Dorsett. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Henshaw Kelly. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* Roy Grogan. *Secretary,* J. McIver, 714 Medical Arts Building, Dallas, Texas.

Michigan Society of Obstetricians and Gynecologists (formerly the Detroit Obstetrical and Gynecological Society). *President,* H. C. Walser. *Secretary,* Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. *President,* Francis R. Irving. *Secretary,* Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* T. M. Boulware, Birmingham, Ala. *Secretary,* John Newdorp, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. *President,* Glen N. Rotten. *Secretary,* R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.

Books Received

THE DOCTORS MAYO. By Helen B. Clapesattle. Illustrated. The University of Minnesota Press. Minneapolis, 1941.

THE MICROBE'S CHALLENGE. By Frederick Eberson, Ph.D., M.D., Director of Laboratories, Gallinger Hospital, Washington, D. C. 354 pages. The Jaques Cattell Press, Lancaster, Pa. 1941.

ABOUT OURSELVES. By James G. Needham. 276 pages with illustrations by William D. Sargent. The Jaques Cattell Press, Lancaster, Pennsylvania, 1941.

CONTRIBUCION AL ESTUDIO DEL EMBARAZO ABDOMINAL. Por Dr. David Orta Menendez. Faculdad de Medicina de la Universidad de la Habana. Tesis de Instructor, 1939.

THE TOXEMIAS OF PREGNANCY. By William J. Dieckmann, Associate Professor of Obstetrics and Gynecology, University of Chicago, etc. 521 pages, with 50 text illustrations and three color plates. The C. V. Mosby Company, St. Louis, 1941.

CLINICAL IMMUNOLOGY, BIOTHERAPY AND CHEMOTHERAPY. By John A. Kolmer, Professor of Medicine, Temple University School of Medicine, etc., and Louis Tuft, Assistant Professor of Medicine, Temple University School of Medicine, etc. 941 pages, illustrated. W. B. Saunders Company, Philadelphia, 1941.